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AN EPIDEMIC OF INFECTIVE HEPATITIS IN BIJAPUR DISTRICT (BOMBAY PROVINCE)

T. B. PATEL, M.B.B.S., B.SC., B.HY. (BOMB.), D.P.H. (LOND.),

Assistant Director of Public Health, Poona (Bombay Public Health Service).

EPIDEMIOLOGY

Numerous epidemics of this disease have been reported from different parts of the world. During the second World War it assumed a special importance due to its widespread occurrence among the troops of different nationality. European troops were found to be more susceptible than others. Incidence of this disease has been variously estimated from 1 to 5 per cent in different countries, while mortality rate has been from 0·1 to 1 per cent. Very few epidemics of this disease have been reported among the civilian population in this country. Due to its benign nature and as an individual practitioner comes across only a few cases, it seems to have escaped notice. The average Indian seems to be less susceptible to it. However if general practitioners and health authorities would remain on the look out, probably it will be reported more often. A similar position has been reported from Ceylon (Jaywardene, 1945).

During the month of September, doctors in Bagalkot town in Bijapur district with a population of 25,000, noticed cases of jaundice in unusual number and these began to crop up in an increasing proportion during the following months. They could not explain the reason for this. Some thought that they might be due to malaria. It was found that malaria was prevailing in an epidemic form in some of the adjoining hyper-endemic areas. But no case was detected in Bagalkot. On detailed inquiry the clinical course of the disease well fitted in with an epidemic of infective hepatitis, described in other countries. It was agreed upon that the doctors should report all cases of jaundice that they might come across in their practice with details regarding the history, clinical signs and symptoms of each case. Thus all the fifty-nine cases were reported by this voluntary notification, forty-seven by doctors in Bagalkot town, including four from three adjoining villages and twelve by the dispensary medical officer of Bilgi, a town fourteen miles away from Bagalkot, with a population of 5,000. Five in the latter were from villages near Bilgi town. A circular was sent to all medical officers to remain on the look out for cases of jaundice. However none were reported from other parts except the above area. Distribution by sex, age group and months of these fifty-nine cases is given in Tables I and II below:

TABLE I—SHOWING INCIDENCE BY AGE AND SEX

Age group	*No of cases*		
	M.	F.	Total
0- 5	2	3	5
6 15	9	5	14
16-25	10	8	18
26-35	7	3	10
36-45	7	0	7
46 onward	5	0	5
	40	19	59

TABLE II—SHOWING INCIDENCE BY MONTHS

Months	*Year*	*No of cases*
August ..	1944	5
September ..	„	8
October ..	„	18
November ..	„	26
December ..	„	2
January ..	1945	nil
		59

Peak incidence was found in the months of October and November. By January the epidemic had come to an end and no case was noticed in spite of close inquiry. A similar seasonal incidence during autumn and early winter has been reported from other parts, (Damodaran and Hartfall, 1944, Banerji, 1945, Gowen, 1945). The highest number of cases were in age group 16 to 25. There were four families with two cases in each. Ten cases were reported from the school children among the primary schools. In one school, the school master and his wife were affected in the early part of the epidemic. There were five cases, later on in that school.

The disease is generally believed to be due to a filtrable virus and spreads by droplet infection during close contact. Successful transmission experiment of the disease among the human volunteers by oral administrations of fæces and urine from cases of infective hepatitis have been described. Flies, contaminated food and utensils, water etc., may also play a part in its spread.

Incubation period varies from three to six weeks. In our series in two cases observed in two families it was 22 days and 28 days respectively. A person is

infective during a part of incubation period, pre-icteric stage and also part of the icteric stage. The case is highly infective during the pre-icteric stage. Usually there is a high degree of immunity after an attack. However relapses have been noticed to occur. There were no relapse in the present series.

Occurrence of jaundice after arsenical treatment from improperly sterilised contaminated syringes, after taking blood samples for examination, after injections of convalescent serum, (homologous serum jaundice), and after yellow fever vaccine have been described. This has been ascribed to a different icterogenic virus with a longer incubation period and is not considered here.

Clinical Course

The clinical course may be divided into two stages, *viz.*, (*a*) Pre-icteric stage, and (*b*) Icteric stage.

Pre-icteric stage—During the first stage the attack starts usually insidiously with headache, pains all over the body and chill or shivering. The temperature rises from 99°F to 100°F and may go upto 101°F to 102°F on the third day. There is marked anorexia and nausea and vomiting may develop early. There is also tenderness of liver in some cases and the liver may be enlarged.

Icteric stage—This develops from four to seven days after the onset of fever. In most cases fever comes down on fourth or fifth day when the yellowness is noticed in conjunctivæ. Stools in many cases are pale while urine is of deep colour and bile salts and pigments are present in it. The patient usually feels better and there is improvement in the condition though the yellow tinge may become deeper and extend over the whole body.

In the present series anorexia was noticed in thirty-two cases (59 per cent), nausea and vomiting in fifteen cases (25 per cent), headache and general body-ache in fifteen cases (25 per cent), deep coloured urine in twenty-one cases (35 per cent), pale stools in thirteen cases (22 per cent), liver tender and/or enlarged in twenty-one cases (35 per cent), spleen enlarged in four cases (6 per cent). Itching was not complained of while bradycardia was found in a small proportion of cases.

In a few instances the cases were ambulatory with no fever or any other symptom and were recognised only from the icteric tinge in the eyes noticed by the patient's friends or relatives. One patient had hæmorrhagic symptoms. This patient had a severe attack and it was reported by the doctor that the patient had taken alcohol during illness. He recovered after a fortnight's stay in the dispensary though the icteric tinge in the eyes persisted for a long time. Alcohol has been found to increase the susceptibility as well as severity of attack. (Damodaran and Hartfall, 1944).

Diagnosis

This was mainly arrived at on clinical grounds. Signs and symptoms were identical with those described in other epidemics. Marked anorexia, low to moderate fever, tenderness in the liver region and improvement in general condition with the development of jaundice were quite a characteristic feature. In some suspicious cases blood smears were taken for excluding malaria. In a few cases in which blood examination was made there was found a relative lymphocytosis. In jaundice due to Weil's disease high fever, marked prostration and leucocytosis is present and isolation of leptospira from urine or blood agglutination confirms the diagnosis.

Treatment

Usual routine treatment with rest in bed, a saline purgative and alkaline mixture was given. In some severe cases diet was restricted to milk in the beginning. No restrictions were adopted regarding the fatty foods in the diet. In severe cases glucose was given intravenously. The amino-acid methionine has been known to be of value, in protecting the liver from damage in experimental animals. Recently protein hydrolysate has been reported to be of value (Vishwanathan, 1945).

Summary and Conclusions

(1) An epidemic of infective hepatitis in two small towns and adjoining villages in a rural area of Bijapur district is described.

(2) Highest number of cases occurred during the months of October and November and children and young adults were affected in a greater number than others.

(3) The disease is likely to be more often noticed if looked for.

(4) The epidemic was of a mild type and there was no fatality.

Acknowledgments

I take this opportunity to thank the Secretary, Dr. W. G. Bhagwat and other members of the Bagalkot Medical Union, Dr. B. M. Joshi in charge of Bagalkot Medical dispensary and Dr. Pandit in charge of Bilgi dispensary, for their willing co-operation and help in showing me the cases and supplying me with the details regarding them.

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LOEFFLER'S SYNDROME

(With a Case Report)

D. S. SETHNA, M.B.B.S., F.C.P.S.,

King Edward Tuberculosis Sanatorium, Dharampur

Since 1931 when Loeffler first described transient pulmonary infiltrations with blood eosinophilia, much work has been done and the various factors differentiated by different authors. Today although the syndrome remains in its full entirety as first enunciated by Loeffler, the various etiological factors are gradually being evolved as more and more cases come under observation. To start with, Sisson and Voget in the year 1929 discovered pulmonary densities associated with a case of anaphylactic shock (following antitetanic serum injection). Loeffler associated the syndrome to an allergic nature. Stefano came across a case with amœbæ in the sputum. Engel of Shanghai in 1935 brought forth the epidemic pulmonary infiltration due to the pollen of Privet. Next came ascaris on the scene, followed by Trichinella, and Fasciola hepatica. Hermann in 1933 brought forth the relation of intrapulmonary changes in periarteritis nodosa. Allergic rhinitis and paranasal sinusitis seem a common finding.

The syndrome described by Loeffler consists of (*a*) history of frequent attacks of upper respiratory infection, (*b*) attacks of asthma increasing in severity with the spread of the pulmonary lesion, (*c*) low fever, (*d*) cough and dyspnœa, (*e*) fatigue, (*f*) eosinophilia 10-60 per cent, (*g*) sedimentation rate slightly raised, (*h*) the physical examination is negative except for a few pulmonary signs like sibilant rales over an area of consolidation. The last but the most important is roentgenological finding. Opacities single or multiple, unilateral or bilateral, from minimal mottling to extensive pneumonic patches can be seen. The most important finding is that these so-called infiltrations vanish like magic to reappear at some distant spot or involve the opposite lung, and yet the radiological findings are quite disproportionate to the subjective features of that particular case.

Loeffler's syndrome is of great importance to the phthisiologist for it mimics tuberculosis of the lungs very well, and patients have been sent to sanatoria for treatment over and over again till diagnosed later on. In its insidious onset, and its early radiological findings it mimics tuberculosis but for the fact that (*a*) tubercle bacilli are never found in the sputum, (*b*) tuberculin test is negative, (*c*) symptomatology contradicts the radiological findings, and lastly (*d*) radiological findings disappear like magic.

The case reported below was sent to a sanatorium and treated for tuberculosis. Finding his sputum negative, and his general condition good he was advised to continue sanatorium regimen at home. He then came to us being admitted for tuberculosis. Except for one symptom he could be classed under this syndrome. There are three points which I shall mention at the start, (*a*) he is allergic to the rays of the sun, (*b*) he gives a history of infection with amœbæ, hook worms and ascaris, (*c*) his radiological findings are as described above. In Loeffler's syndrome asthma plays an important role, and here comes the rub for this patient has never had asthma. Can hook worm infection cause this syndrome as it had been found with amœbæ in his stools?

Case report—Mr. M.L.G. was admitted to this institution on 25-9-45. His history is very important and runs as follows. At the age of two years his mother died of pulmonary tuberculosis. When 4 years old he had severe bronchitis for quite a long time which left him weak and rickety. This constitution remained till the age of 21. In June, 1939, because of anorexia and mucous diarrhœa his stools were examined and found to contain Ent. histolytica. Emetine 3 grains were injected and a course of enterovioform given by mouth. Gastric upsets and mucous stools occurred off and on once every three months till the year 1945. This shows clearly the disadvantage of playing with emetine in the early stages of amœbiasis. In June, 1944, he had small-pox. In July, 1944, because of weakness his stools were again examined. They showed amœbæ and hook worms, his sputum was negative to T.B. Emetine gr. 3, enterovioform, and carbarsone were given. He was also treated for hook worms. In February, 1945, he spat blood (not coughed up). His sputum was examined and found suspicious to tubercle bacilli. X-ray was taken on 15-3-45 and found vaguely suspicious. The evening temperature, he now noted, ran up to 99°F. In April, 1945, he entered the above sanatoria. Anorexia, weakness, and temperature up to 99°F. were his complaints. His weight was 98 lbs. He had no cough or expectoration. On admission his sedimentation rate was 5/200 mm. for 1 hr. X-ray picture taken on 6-4-45 showed prominent bronchial markings, more so on the right. X-ray taken on 9-7-45 revealed peribronchial fibrosis with infiltration to the right base from the hilum showing further spread. He was now walking about and sputum remained negative right throughout his stay there. His sputum and B. S. R. were perfectly normal from start to end. His temperature disappeared from the month of July, 1945. He left in August, 1945. He was advised gold treatment and rest. On 4-9-45 he was x-rayed and the report runs as follows: Right lung shows suspicious areas of infiltration at the base. Left shows infiltration and fibrosis in the left infraclavicular region. On 14-9-45 his sputum was negative to T.B. On 15-9-45 his stool report showed ascaris and Entamœba histolytica cysts. He was again treated for ascaris. Emetine 3 gr. were also given. W. R. in 1944 was definitely negative.

On admission he had no symptomatic complaint. On thorough clinical examination we found nothing abnormal in all the systems specially the respiratory. Urine and stools showed nothing abnormal. His stool was examined repeatedly, persistently showing a normal picture. His sputum was negative to tubercle bacilli in ordinary smear, and on Loewenstein culture medium so also his stomach wash. Tuberculin tests (P.P.D.) also proved negative. This is a very important point. His temperature from the start remained normal. His blood examinations showed

on admission (1) B. S. R. 3/200 mm. 1 hr. (2) Total W.B.C. 12,000 (3) Eosinophilia 16 per cent. After a full course of emetine his blood showed the following changes: (1) B.S.R. 3/200 mm. 1 hr. (2) Total W.B.C. 9,000 (3) Eosinophilia 4 per cent. On microscopic examination the first slide showed well stained eosinophilic cells and after the course of emetine showed degenerated forms with very poor staining. His blood examination leads us to the conclusion that he may be a case of Loeffler's syndrome with amœbiasis as the etiological factor. Nay, it may be due to infestation with hook or round worms. The x-ray findings are as follows:

15-3-45—Lung fields show prominent broncho-vascular markings at the right base.

The following two are records of the above sanatorium as the plates have not been given to the patient.

6-4-45—Bronchial markings present more so on the right.

9-7-45—Peribronchial fibrosis with infiltration to the right base from the hilum.

From this report I conclude that there were definite findings at the right base.

The three reports given below are from the x-rays with us.

3-9-45—*Right*—Mottling with generalized haze in the right infraclavicular zone with mottling scattered in the midzone and base. *Left*—Scattered gross mottling in infraclavicular zone with generalized haze.

18-10-45—*Right*—Haze completely disappeared. Suspicious fine mottling in the mid zone. *Left*—N.A.D.

15-12-45—This picture was taken here, and shows a more or less normal picture with a vague suspicion of mottling in the right midzone.

From the above findings one starts with a perfectly normal picture. Then in the sanatorium report of two months later one finds there is a definite progress to the right base. Another two months show changes in the right infraclavicular zone, base and left infraclavicular zone. After another one month every thing seems to have cleared up. These vague fleeting shadows which vanish like snow against the desert sun is typical of Loeffler's syndrome.

X-rays clinched our diagnosis. Moreover, he had another very important complaint. He was allergic to the rays of the sun, and even walking for a minute or two in the sun produced severe erythema, itching, and when the reaction was very severe a few tiny vesicles—all of which disappeared totally within a period of an hour or two.

To summarise: here is a patient with (*a*) history of amœbiasis, hook worm and ascaris infection, (*b*) allergic to the rays of the sun, (*c*) eosinophilia in the blood, (*d*) radiological findings agreeing to Loeffler's syndrome and (*e*) the last but not the least important is his complete negative reports on investigations for tuberculous disease of the chest.

Acknowledgment—My sincerest thanks to Dr. F. S. Master, our Medical Superintendent for allowing me to publish his case.

PENICILLIN IN PNEUMONIA DUE TO STREPTOCOCCUS VIRIDANS AND STREPTOCOCCUS HAEMOLYTICUS

K. U. JHATAKIA, M.D.,

Hony. Asstt. Physician, Sir J. J. Hospital, Tutor in Medicine, Grant Medical College & Research Worker, Sir Hurkisondas Hospital, Bombay

I intend to present here the case reports of three cases of pneumonia, two due to streptococcus viridans and one due to streptococcus hæmolyticus, which did not respond to sulphonamides and were cured by penicillin. Pneumonia due to streptococcus viridans is an uncommon disease and it is even less commonly diagnosed, as we do not get sputum examined or cultured in each case of pneumonia. It is most often confused with primary atypical pneumonia of virus origin. A few important features of this type of pneumonia due to streptococcus viridans, should be borne in mind.

The disease is characterised by prolonged severe cough, severe pleural pain and thick mucoid sputum. Mortality is also very high. 4 cases out of 5, reported by Solomon, and Kalkstein (1943), died. Lesion is lobar and involves more than one lobe, either together or one after the other. White blood court may or may not rise. Patient is acutely ill. Bacteremia is common but has no effect on prognosis.

Diagnosis on purely clinical grounds is very difficult, and so many cases must have been mistaken for severe types of pneumococcal pneumonia. But if we resort to detailed examination of sputum including the cultural examination in every case of pneumonia which does not respond well to sulphonamides in 48 hours' time, we are likely to detect in future more cases of pneumonia due to streptococcus viridans. When a patient does not respond to usual sulphonamide therapy, one has to think whether:—

(1) Sulphonamides are given in adequate dosage.

(2) They are well retained and absorbed.

(3) Organisms are either sulphonamide-resistant or insensitive.

(4) Patient is too low to put up any fight against the infection etc.

If one always investigates such cases in this manner, one is likely to diagnose this infection more frequently now than in the past.

The usual rapid method of sputum typings by the capsule swelling pneumonia will fail to disclose the streptococcus viridans. Sputum culture on blood agar is essential for isolation. Mouse inoculation followed by plating of peritoneal exudate of the mouse is also a satisfactory method. The bile solubility test may be performed to differentiate pneumococcal from streptococcal colonies, since only the former are bile soluble.

The clinical picture taken in conjunction with the findings of streptococcus viridans in sputum in pure culture is sufficiently convincing data to warrant the diagnosis of streptococcus viridans pneumonia. The infection does not respond to sulphonamides so well as it does to penicillin.

Case 1—A Hindu patient HC. aged 29 years was admitted on 7-9-45, in our wards with high fever and

in semiconscious condition. Temperature was 103°F. Pulse 140 p.m. and respiration rate 42 p.m. On examination of the respiratory system, there were impaired note in the left axillary area and on back and bronchial breathing with few crepitations in same area. Blood pressure 118/70 m.m.Hg. Other systems were quite normal. C.N.S. was also normal except drowsy condition of the patient. Blood examination showed white blood cells, 4,000 per c.mm. and red blood cells, 3·1 million per c.mm. with hæmoglobin 52 per cent.

The patient was put on usual treatment with sulphadiazine 4 tablets stat and 2 tablets 4-hourly, along with alkaline diaphoretic mixture. On 8-9-45, he developed retention of urine which responded to carbachol injection. General condition remained same. Sulphadiazine had no effect at all and patient developed consolidation signs on right middle zone also. As it did not respond to sulphonamide, and there was leucopenia, the sputum was cultured. Organism reported was streptococcus viridans. On 10-9-45, night, penicillin in 20,000 units 3-hourly doses was started by I.M. injections and sulphadiazine was omitted. On 11-9-45, temperature dropped to 99°F. going upto 100·5°F. in the evening. General condition improved a lot. Since 12-9-45, the temperature remained normal, there was no more retention of urine and general condition was much better. Total penicillin used was 3,00,000 units only during 48 hours. Due to scarcity of penicillin, I stopped penicillin on 12-9-45 and again started sulphadiazine in 2 tablets 6-hourly dosage hoping that it might help at this stage. It was gradually reduced to 1 tablet 6-hourly on 4th day. Total 30 tablets were given in 4 days. Blood pressure had come down during this illness from 110/70 to 100/50. Patient gradually recovered completely. Interesting points in this case were:

(1) Cause of pneumonic consolidation was not pneumococci but streptococcus viridans, which alone grew in sputum culture.

(2) Infection involved both lungs in 4 days.

(3) Infection did not respond to sulphadiazine but quickly responded to penicillin.

(4) Blood count showed leucopenia.

(5) Patient was acutely ill and looked very weak for a few days after the temperature was normal.

(6) Patient had toxic retention of urine.

Case 2—A male, Christian, aged 23 years was admitted on 16-12-45 in our wards for continuous fever for 4 days, cough and pain in left side of chest. He started with fever with rigor. Patient was drowsy on admission. Temperature 103°F. Pulse 142 p.m. and respiration rate 42 p.m. On examination there were signs of consolidation on left base. The tongue was coated and there were signs of toxæmia. Blood pressure was 120/75. Blood examination showed total white blood cells, 7,500 per c.mm.; differential count: polymorphonuclears 87 per cent, lymphocytes 10 per cent, large mononuclears 3 per cent; no malarial parasites were detected. As he was very drowsy and had few convulsions lumbar puncture was done but C.S.F. was quite normal on examination.

Routine pneumonia treatment was started with usual dose of sulphadiazine 4 tablets to start with and 2 tablets 4-hourly. As he was toxic, drowsy and getting convulsions, hypertonic glucose solution was given on 17-12-45, temperature was between 101° and 103°F. all day and general condition remained the same. On screening consolidation at left base was confirmed. On 18-12-45 the sputum was examined for organisms and was cultured. On simple examination pneumococci and streptococci were reported but on culture pure growth of streptococcus viridans was obtained. Temperature was 103°F. and respiration rate 52 p.m. and cyanosis appeared. General condition was unsatisfactory. Sulphadiazine was omitted and I.V. glucose, coramine and vitamin C were given. Oxygen was given continuously.

On 19-12-45, the temperature was 99·4°F. Respiration rate was 36 and pulse 120 p.m. Patient was still drowsy. The signs in the lungs were same, cyanosis persisting. Penicillin was given in same usual dosage. On 20-12-45, the temperature was 99F., pulse 104 and respiration rate 28 p.m. The general condition improved. The lungs showed same consolidation signs. Penicillin was continued. 22-12-45—the temperature was normal, pulse 100, better in volume and tension. The patient was conscious but could not speak or swallow anything. Patient was seen by E.N.T. specialist and no œdema or other abnormality was detected in throat.

During the period from 22-12-45 to 24-12-45, the temperature remained normal. Penicillin was stopped on 23-12-45. Total 7,00,000 units were given in 4½ days. Left base consolidation started resolving. On 25-12-45, patient got fever with rigor.

In the morning the temperature was 102°F. which rose to 104·6°F. in the evening. Difficulty of speaking and swallowing had persisted and the patient was getting nasal feeds all these days. Blood smear did not show any parasite. Patient was given one quinine injection intramuscularly and sulphadiazine was also started in the evening. On 26-12-45, the patient was screened and fresh consolidation in left middle zone was detected while left base was getting clear. Patient was again seen by E.N.T. specialist for difficulty in swallowing but no obstruction or any change was detected in throat. There was no paralysis of any muscle of deglutition.

On 26-12-45, the temperature was 101°F., pulse 118 p.m., respiration rate 38 p.m. Penicillin was again started in 20,000 units 3-hourly doses I.M. along with sulphadiazine.

On 27-12-45, the temperature came down to normal. General condition improved. Penicillin and sulphadiazine were continued.

On 28-12-45, the temperature remained normal. Penicillin was stopped and sulphadiazine was reduced and was stopped on 29-12-45. Total 3,00,000 units of penicillin were given this time. Patient started swallowing food on 30-12-45 and made an uneventful recovery and was discharged on 16-1-46.

The interesting points in this case were:—

(1) High toxicity of the patient on admission.

(2) No response to sulphadiazine but the case responded gradually to penicillin.

(3) Creeping type of infection—base to start with and later on midzone on same side.

(4) Retention of urine for two days during acute illness.

(5) Patient developed inability to speak or swallow in absence of any lesion detected in throat. This could not be explained satisfactorily.

(6) Very gradual recovery from the illness.

Case 3—This is the case report of pneumonia due to streptococcus hæmolyticus. A Muslim male aged 18½ years was admitted on 21-9-45, for continuous fever for 9 days, cough with expectoration for 6 days. The temperature was 101°F., pulse 100, and respiration rate 30 p.m. On examination, there were signs of consolidation on right side of chest, affecting nearly the whole lung; blood pressure was 126/100. Other systems were normal. The patient was given usual treatment with sulphadiazine, 4 tablets stat and 2 tablets 4-hourly. On blood examination, total white blood cells count was 8,000 per c.mm. On screening, lesion was confirmed. On 22-9-45, the temperature was 103·8°F., pulse 126 p.m. and respiration rate 40 p.m., delirium persisting. Patient showed slight rigidity of the neck and so lumbar puncture was done. C.S.F. was found normal on examination. Sulphadiazine was continued along with alkalies. On 24-9-45, temperature 102°F., pulse 110 p.m. and respiration rate 54 p.m., general condition was poor and delirium persisted. Patient developed retention of urine, sputum examination showed streptococci; sputum culture showed growth of streptococcus hæmolyticus. Penicillin in 20,000 units 3-hourly doses I.M. was started and sulphadiazine in small doses was continued.

On 25-9-45, the temperature came down to normal. Patient started passing urine, and general condition improved much. Blood pressure was 102/65 and so he was given cortical extract. Delirium disappeared. The patient then had uneventful recovery. Total 3,00,000 units of penicillin were injected in 2 days, and total 45 grams of sulphadiazine were given during 11 days. Interesting points in this case were:—

(1) Pneumonia was due to streptococcus hæmolyticus, which did not respond well to sulphadiazine while promptly yielding to penicillin.

(2) Patient developed delirium probably due to sulphonamides.

(3) Patient had retention of urine during acute illness which disappeared of its own.

(4) Whole right side of the lung was involved.

(5) Long duration of the disease—Fever lasted for 15 days inspite of chemotherapy.

These reports stress the necessity of culturing of sputum in all serious cases of pneumonia. Secondly penicillin should be immediately started in such cases. Penicillin is at present costly and scarce and so its indiscriminate use should be avoided wherever laboratory facilities are available. Most pneumococcal pneumonias will yield to sulphadiazine and in such cases if we know definitely the causative organisms, penicillin can be spared while in other cases where

(*Concluded at foot of col. 2*)

PENICILLIN IN CHANCROID*

K. D. LAHIRI, M.B., B.S.,

Senior Hony. Medical Officer, Skin & V. D. Dept., Patna Medical College Hospital

The use of penicillin in the infection with Ducrey's bacillus has not been reported by any venereologist in India and none so far appear to have worked in this direction abroad. Early in 1945 it was suggested that the chancroidal infection should yield to this new antibiotic (Lahiri, 1945).

The author's attention was drawn in this direction while treating a case of mixed infection in June, 1945, where the patient showed positive Ito-Reinsterna's test for Ducrey's bacillus infection and the smear from the penile sore revealed the presence of Gram-negative short-chained, rod-shaped strepto-bacillus of Ducrey and the dark-ground examination showed Treponema pallidum and the urethral smear showed Gram-negative diplococci, resembling Neisseria gonorrhœæ together with numerous pus cells. The patient was treated with penicillin when all the ulcers healed up and urethral discharge became negative with the disappearance of N. gonorrhœæ and the threatened right inguinal bubo disappeared. Dark-ground examination became negative too on repeating thrice but the blood Wassermann reaction was doubtful, which on repeating after one week became positive.

The above case made me think whether it would be possible to use penicillin in chancroid, but for about three months, for want of ample supply of penicillin it was not possible to use penicillin in chancroid except in two cases where patients could secure penicillin and the result was very encouraging but during September to December 1945 I could treat a fair number of cases of pure chancroid with penicillin alone or combined with sulphonamide as follows:—

* Read at the Scientific Section, XXII All-India Medical Conference, Amritsar, December 1945.

(*Concluded from col. 1*)

the organisms are sulphonamide-resistant, and penicillin sensitive, penicillin can be immediately started. It has been observed that sulphadiazine in pneumococcal pneumonia in adults is as good in effect as penicillin, but in older persons penicillin is definitely superior to the sulpha group. The use of penicillin in old persons is thus more justified in the majority of cases. The use of penicillin in all cases of pneumonia will be justified only when cheap oral preparations of penicillin will be available in the market.

I am much thankful to my house-physician, Dr. G. G. Vashi, M.B.B.S., for preparing case records and to the superintendent, J. J. Hospital, Bombay, for permission to publish them.

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TABLE I—SHOWING RESULTS OF PENICILLIN TREATMENT IN PURE CHANCROIDAL INFECTION

No.	*Name*	*Duration in days*	*I. R. test*	*Gram stain*	*Dark-ground exam.*	*Serum W.R.*	*Total Penicillin in lacs*	*Time of cure in hours*
1.	R.C.	3	Positive	Negative	Negative	Negative	3	18
2.	M. H.	2	do	do	do	do	2	16
3.	S. S. M.	6	do	do	do	do	2	14
4.	S. I. A.	17	do	do	do	do	1½	16
5.	R. C. P.	11	do	do	do	do	1	15
6.	L. P. S.	9	do	do	do	do	1	15
7.	R. P.	26	do	do	do	do	1½	18
8.	M. A.	20	do	do	do	do	1	12
9.	C. M.	4	do	do	do	do	1	10
10.	S. A.	7	do	do	do	do	1½	12

TABLE II—SHOWING RESULTS OF COMBINED TREATMENT OF CHANCROIDAL INFECTION WITH PENICILLIN AND SULPHA DRUGS

No.	*Name.*	*Duration in days*	*I. R. test*	*Gram strain*	*Dark-ground exam.*	*Serum W.R.*	*Total Sulpha in gm.*	*Total Penicillin in lacs*	*Time of cure in hours*
1.	K. P.	3	Positive	Negative	Negative	Negative	11	2	18
2.	L. P.	5	do	do	do	do	18	2	11
3.	S. S. P.	7	do	do	do	do	10	1	12
4.	K. L.	17	do	do	do	do	8	1	10
5.	M. S.	11	do	do	do	do	6	1	12

TABLE III—SHOWING RESULTS OF TREATMENT OF CHANCROIDAL INFECTION WITH COMPLICATIONS WITH PENICILLIN ALONE AND COMBINED WITH SULPHA DRUGS AND VACCINE

No.	*Name*	*Condition*	*I. R. test*	*Gram stain*	*Dark-ground exam.*	*Serum W.R.*	*Total penicillin in lacs*	*Sulpha-drugs and vaccine*	*Time of cure in hours*
1.	C. P. S.	Bubo with phagedena	Positive	Negative	Negative	Negative	3	Sulpha and vaccine I.V.	36
2.	K. P.	Bubo	do	do	do	do	1	—	28
3.	M. H.	Bubo	do	do	do	do	1	Sulphadiazine 6 gm.	24
4.	R. U.	Phagedena	do	do	do	do	3	Vaccine 1 c.c. I.V.	24

DISCUSSION

By using penicillin alone in Ducrey's bacillus infection one lac units penicillin, dissolved in normal saline, when injected every two hours the ulcer completely heals up in ten hours as will be evident from Table I. The use of sulphonamide compounds could not hasten the cure and the minimum time recorded was ten hours with one lac Oxford units of penicillin and 8 grams of sulphonamide compound (*vide* Table II). In cases of complications, particularly in aborting the bubos, the combined therapy of penicillin with sulphonamide is useful in hastening the cure while in systemic infection where phagedena and bubo have developed, combined therapy of sulphonamide and penicillin with an intravenous injection of Ducrey's bacillus vaccine should be tried (Table III).

For early cases of chancroid it is better to give first a trial with penicillin for at least 12 to 24 hours and if not controlled, a sulpha-drug should be given in combination with penicillin.

Where the patient is infected by Ducrey's bacillus and Treponema pallida penicillin should be continued for a period of two weeks night and day and in cases of Ducrey's bacillus infection with N. gonorrhœæ penicillin should be given three hourly for a period of at least 36 hours.

Penicillin should prove the best drug in the world to control the spread of venereal diseases.

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SPECIAL ARTICLES

PROFESSOR ARTHUR STOLL AND HIS CONTRIBUTIONS TO PHARMACEUTICAL RESEARCH

B. MUKERJI, D.SC., M.D., F.N.I.,

Bio-Chemical Standardisation Laboratory, Government of India, Calcutta

Medical and Pharmaceutical research workers in India are generally acquainted with the scientific contributions of British and American workers, because most of their writings are available in the English language. Continental scientists are hardly known except through cross reference of their published work in English text-books and journals. It might therefore be a welcome departure occasionally to review the life and work of some front-rank continental scientists who have made outstanding contributions to medical and pharmaceutical research of an international standard. The writer has been in rather intimate touch with some phases of the scientific work of Prof. Arthur Stoll for some years and he has often felt that the remarkable achievements of this continental scientist should be more widely known to his Indian colleagues who are working in the field of Indian indigenous drugs. Prof. Stoll would be reaching his 60th birthday next January and this offers, in the writer's view, a fitting occasion for a scientific appraisal of his work—a story which is bound to create an inspiration in the minds of younger Indian workers to emulate his example.

ARTHUR STOLL
(Photo taken in 1936)

Early life and training—Arthur Stoll was born in the Swiss village of Schinznach on the 8th January, 1887. From 1894 to 1903 he went to the local district school, where his father was a Headmaster. After completing his studies here, he joined the County School at Aarau (1906) from where he moved to the Federal School of Technology at Zurich. In 1909, even before he received his Diploma in Natural Sciences (1910) and the Degree of Doctor of Science (1911), he became associated with his teacher, R. Willstaetter, the famous chemist, who later obtained the Nobel Laureate—an association which was destined to lead to many achievements in the field of pharmaceutical and plant chemistry. Willstaetter found in young Stoll a research worker of great promise and began with him the study of Chlorophyll, which later brought Prof. Willstaetter into such international fame. When Willstaetter accepted a call to the newly built Kaiser-Wilhelm-Institute for Chemistry in Berlin in 1912, Stoll followed his teacher and became his first Assistant there. As a result of the joint work, a monograph ("Untersuchungen ueber Chlorophyll") was published by Willstaetter and Stoll in 1913. The association of Stoll with Willstaetter continued even when his Professor went to Munich as Head of the Bavarian Academy of Science. Their joint work in Munich resulted in another book "Untersuchungen ueber die Assimilation der Kohlensaeure" (1917). For this study a highly active preparation of peroxidase was required. The investigation that had to be taken up in this connection was so extensive that the material could be put together in another publication by the same two authors in the same year—"Ueber Peroxydase". This was also the starting point of Willstaetter's long and fruitful study on enzymes, which has laid the foundation of modern enzyme chemistry.

Research Organization and Administration—In 1917, at the young age of 30 years only, Stoll was invited to organise the pharmaceutical department of the 'Chemical works formerly Sandoz' and he decided with the advice of his teacher, to return to his own country to take up a new field of activity. So long he was interested in the organic chemistry of plant constituents but he was now called upon to create a department of pharmaceutical research in a commercial organisation. In consultation with Prof. Willstaetter, he decided from the very beginning to establish a research laboratory of an University calibre inside the commercial organisation—a novel departure from the established practice in commercial firms in those days. He asked for a generous budget provision for his research department and proceeded to get together a group of first-class scientific and technical workers in the fields of enzyme chemistry, pharmacology and chemotherapy. This policy worked so well that within an amazingly short time, Prof. Stoll succeeded in establishing the name and reputation of Sandoz pharmaceutical products all over the world. Simul-

taneously, his reputation as a research director became recognised and he was appointed Royal Bavarian Professor at the University of Basle. In spite of his preoccupation in the research laboratories of the Sandoz Company, where he gradually rose to become the Vice-President and later the President of the Managing Committee, Prof. Stoll continued to take a lively interest in his teaching work at the University of Basle and gave full facilities to the students to visit and work in the Sandoz laboratories thereby exploding the myth of 'trade secrets' in pharmaceutical organizations. By adopting these bold steps, he not only succeeded in bringing the scientific aspects of drug industry to the forefront but encouraged on a wide scale 'collaborative research', then unknown in Switzerland. Indian drug industry can learn a lesson from the example of Prof. Stoll. He was almost the first person in Switzerland who showed that encouragement of research of a university standard in a pharmaceutical concern is not 'money lost', but a sound investment which does bring dividends in the long run.

Ergot Alkaloids

After completing the organisation of the research laboratories at the Sandoz Works, Stoll took up work on the ergot problem. In his previous study on chlorophyll (separation of chlorophyll A and chlorophyll B) and enzymes, Stoll was constantly faced with the problem of working with extremely delicate and complicated substances and this experience proved a great asset in his later research in the field of pharmaceutical chemistry. The observation that the uterus activity of ergot of rye and its extracts diminished during storage naturally indicated that the active substance of the drug must be unstable and extremely delicate. Prof. Stoll decided therefore to try the method of 'protective isolation'*, developed for his chlorophyll studies, on ergot.

As a result of the application of this new method of alkaloid isolation, ergotamine was discovered in 1918. This was the first significant contribution on ergot problem made since the discovery of ergotoxine in 1906 by Barger and Kerr and independently by Kraft. Pharmacologically, ergotamine has all the actions of ergotoxine, but in addition it decreases or abolishes the action of epinephrine on the small intestine (Rothlin, 1925). Ergotamine has already achieved a recognised place in therapeutics, particularly in Migraine, Pruritus and obscure headaches, uses which were not thought of before.

In 1932 an apparently new ergot alkaloid, Sensibamin, was isolated by Wolf, but Stoll proved that it was only a molecular compound of 1 molecule ergotamine and 1 molecule ergotaminine. Later on, Stoll and his collaborator, Burckhardt, showed that 'ergoclavin' also was a molecular complex of ergosine and ergosinine and not a genuine ergot alkaloid.†

The discovery of ergobasine by Stoll and Burckhardt in 1935 coincided with the discovery of ergometrine (Dudley & Moir, England) ergostetrine (Thompson, Baltimore) and ergotocine (Kharasch & Adair, Chicago), in other laboratories. At the beginning the four alkaloids were considered as different from each other, because the physical and analytical data published by the four laboratories did not tally. Stoll's molecular formula was, however, later proved to be the correct one and gave Stoll a certain measure of priority in this group discovery. Stoll's meeting with Sir Henry Dale, Director of the National Institute for Medical Research, London, at the First International Medical Week in Switzerland led to a comparison of the four alkaloids which then established their identity. Another ergot alkaloid, ergocristine and its isomer ergocristinine, was discovered by Stoll and Burckhardt in 1937. The most striking discovery in this field, however, followed in 1942, when Stoll and Hoffmann succeeded in separating 'ergotoxin' into 3 genuine ergot alkaloids: ergocristine, ergocornine and ergokryptine, and thus proved that ergotoxin was not a genuine ergot alkaloid but only a mixture of 3 genuine alkaloids in varying proportion. Two of the three components, ergocornine and ergokryptine, were new alkaloids and their formulæ were established.

Further success came with the partial synthesis of ergobasine (ergometrine) by Stoll and Hoffmann. They started with the hydrazid of racemic isolysergic acid, turned it into its azide, treated the latter with 1-2 aminopropanol-(1) and thus obtained a mixture of the 8 isomers of ergobasine. These were separated, the natural ergobasine being represented by d-lysergic acid-1-propanol-amide-(2). It was found that the other isomers had an inferior action on the uterus compared with natural ergobasine, except one which has about the same activity. It was logical to continue this study by introducing other amino alcohols into the partial synthesis and until the end of 1942, the following new ergot alkaloids, not found in nature, had been synthesized by Stoll: Nor-ergobasine (with amino ethanol), methyl-ergobasine (amino butanol), and isopropyl-ergobasine (with leucinol). Taking the activity of natural ergobasine on the uterus as 1, the activity of nor-ergobasine is 0·3, that of methyl-ergobasine 1·3, and that of isopropylergobasine 0·3. Thus a quickly-acting water-soluble ergot alkaloid, not known in nature, has been synthesized which is more active than the best natural product.

This laboratory research went parallel with studies on the artificial production of ergot of rye under Stoll's supervision. Various methods of inoculating

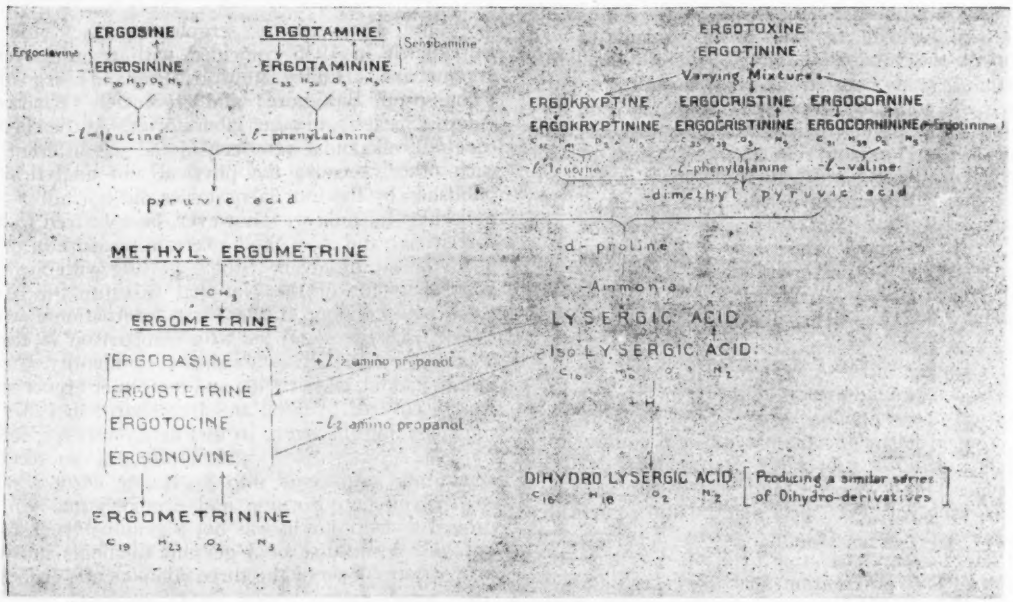
* The method of 'protective isolation' is based on the following principles:—The cell substances has pronounced amphoteric properties. By the moderate addition of mildly acid chemicals, *e.g.* aluminium sulphate, to the drug the basic groups in the amphoteric material are neutralised, while its acid groups are freed without any appreciable change of pH and without the occurrence of soluble free acids. The acidulated material holds the alkaloids so strongly that by exhaustive extraction with organic solvents all the soluble acid and neutral impurities (350-400 gm. in 1 kg. ergot.) are removed without any loss of the alkaloid. The cell material is then treated with alkali and the alkaloid extracted with the same solvents as used for the previous extraction.

† Mukerji, *Indian M. Gaz.*, **73**:355, 1938.

the ears of rye with laboratory cultures of the fungus, *claviceps purpurea,* were developed including very efficiently working machines. Ergot has already been artificially cultivated in India* and some of these machines may be usefully employed in increasing the area under cultivation, in the Nilgiris, Kodaikanal and elsewhere.

The present status of knowledge about the ergot alkaloids is given in the chart below which is derived largely from the work of Stoll.

CHART SHOWING CHEMICAL RELATIONSHIPS OF THE ERGOT ALKALOIDS



OPTICAL ACTIVITY AND FORMULAE OF THE "NATURAL" ALKALOIDS OF ERGOT

Alkaloid	*Formula*	$[\alpha]_D^{20}$ *in chloroform*
1. *Ergotamine Group*		
Ergotamine	$C_{33}H_{35}O_5N_5$	−155°
Ergotaminine		+385°
Ergosine	$C_{30}H_{37}O_5N_5$	−161°
Ergosinine		+420°
2. *Ergotoxine Group*		
Ergoscristine	$C_{35}H_{39}O_5N_5$	−183°
Ergocristinine		+371°
Ergokryptine	$C_{32}H_{41}O_5N_5$	−187°
Ergokryptinine		+408°
Ergocornine	$C_{31}H_{39}O_5N_5$	−188°
Ergocorninine		+409°
3. *Ergometrine Group*		
Ergometrine	$C_{19}H_{23}O_2N_3$	− 44°
Ergometrinine		+414°

Notes.—(*i*) The optical activities of ergocristine and ergocristinine are stated in the earlier literature to be −186° and +365° respectively.

(*ii*) The chemical formula and optical activity of ergotoxine and its isomer ergotinine were previously given as $C_{35}H_{39}O_5N_5$ and −197° and +365° respectively.

BELLADONNA ALKALOIDS

Stoll's method of 'protective isolation' first used on ergotamine, was further applied to belladonna and thus a total alkaloidal preparation 'Bellafoline' was obtained which contained the total complex of pure lævorotatory belladonna alkaloids in the same form as they occur in the fresh plant. Ordinary methods of isolation are known to yield atropine, hyoscyamine and hyoscine. Though a number of synthetic drugs in the belladonna group are now known, *e.g.,* Homatropine, Syntropan, etc., it is held by many clinical authorities that naturally occurring belladonna alkaloids possess a wider range of therapeutic usefulness than the synthetic and breakdown products.

CARDIAC GLYCOSIDES

Squill bulb—The starting point of Stoll's work on the cardiac glycosides was squill and at the beginning of Stoll's investigation, no one had a clear concept of the nature of its active principles. The close resemblance in the physiological action of foxglove (digitalis) and squill had already led to the assumption that squill also contained cardiac glycosides. The characteristic colour reactions of the digitalis glycosides, however, proved to be negative in the case of squill extracts and a special colour reaction for squill glycosides had to be developed.

The isolation of a pure native squill glycoside was achieved by Stoll and Suter in 1921 and was introduced into therapeutics under the name of 'Scillaren'. However, more detailed publications on the subject appeared only in 1927 after long and difficult chemical and physical studies. It was found

*MUKERJI & DEY, *Current Science,* **12**:3, 1943.

that the previously isolated complex could be split into two fractions, the easily water-soluble 'Scillaren B' representing about 1/3 of the complex and the purely crystallised but very badly soluble 'Scillaren A' representing 2/3. On account of the better stability against hydrolytic agents, Scillaren B was then used for the preparation of ampoule solutions, whereas the complex of A and B was used for the preparation of tablets. It is probable that Scillaren B again is a complex of at least two components and further progress in the isolation of these components are in progress in Prof. Stoll's laboratories.

The study of the squill glycosides had, amongst other things, revealed that the red variety of African squill contained a specific rat poison. Three publications in the years 1941, 1942 and 1943 by Stoll and his co-workers, Renz and Helfenstein, described the isolation and complete chemical elucidation of this principle which was called 'Scillarosid'. It proved to be of the same elementary structure as Scillaren, but while it has good cardioactive properties, the specific raticidal property is not due to a heart effect. The red variety of squill has apparently not been reported from India. On the other hand, the common Indian squill (*urginea indica*) is a recognised substitute of the 'official' squill.

Digitalis leaves—As early as 1918, Stoll had tried to apply his method of protective isolation also to *Digitalis purpurea* but he obtained complicated mixtures which could not be crystallised and which were not identical with the already known glycosides: digitoxin, gitoxin and gitalin. After having gained more experience with the isolation of the squill glycosides, Stoll, assisted by Kreis, obtained the genuine Purpurea Glycosides A and B. He showed that by enzymatic removal of a glucose group these glycosides could be degraded into digitoxin and gitoxin respectively. Then the study was extended to *Digitalis lanata* and soon the 3 native lanatosides (A, B and C) were isolated and their complex in constant proportion introduced into therapeutics under the name of 'Digilanid'. Stoll proved that Lanatosides A and B could be transformed into the Purpurea Glycosides A and B, by mild alkaline removal of an acetyl group, and he found further that the desacetylation product of Lanatoside C had no parallel in *Digitalis purpurea*. This degraded product could, however, be turned into digoxin by removal of a glucose group.

These findings put the chemistry of digitalis glycosides on an entirely new basis. Until the work of Stoll, it had escaped all the chemists working in this field that they had not isolated genuine glycosides but merely cleavage products, which may already occur when the product is merely dried. Also therapeutically, the discovery had considerable importance because it was found that the genuine glycosides with their additional glucose (and acetyl) groups were better tolerated and had, generally speaking, more favourable properties than the degradation products.

Another series of studies covered *'Strophanthus kombe'* and resulted in the isolation of k-strophanthosid B, the main glycoside of the drug. The first publication on this subject appeared in 1937. Also here the glycoside isolated represented the genuine glycoside as it occurs in the fresh drug, whereas all the other glycosides of Strophanthus previously known had only represented breakdown products.

In 1939, a further publication by Stoll and Renz appeared on the genuine cardio-active glycoside of

SOURCE AND COMPONENT CHEMICAL PARTS OF THE MAJOR CARDIAC GLYCOSIDES
Compiled from data presented by Stoll (1937, 1939)

Source	*Glycoside*	*Sugar*	*Aglycone*
DIGITALIS PURPURA			
Leaves	deacetyldigilanid A —glucose=digitoxin	3 digitoxose	digitoxigenin
	deacetyldigilanid B —glucose=gitoxin	3 digitoxose	gitoxigenin
	gitalin	2 digitoxose	gitaligenin
Seeds	digitalin	glucose and digitalose	dianhydrogitoxigenin (digitaligenin)
DIGITALIS LANATA			
Leaves	digilanid A —glucose & acetyl=digitoxin	3 digitoxose	digitoxigenin
	digilanid B —glucose & acetyl=gitoxin	3 digitoxose	gitoxigenin
	digilanid C —glucose & =digoxin	3 digitoxose	digoxigenin
STROPHANTHUS			
S. sarmentosus	sarmentocymarin	sarmentose	sarmentogenin
	ouabain	rhamnose	ouabagenin
S. gratus	k-strophanthin-β (strophanthin)	glucose and cymarose	strophanthidin
S. kombé	k-strophanthoside	2 mol. glucose and cymarose	strophanthidin
SQUILL	scillaren A	glucose and thamnose	scillaridin A
PERIPLOCA GRAECA	Periplocin	Cymarose	Periplogenin
	Periplocymarin		

Periploca græca—periplocin. This glycoside was isolated in its genuine form and obtained in definite crystals and its structural formula including its sugar chain was fully established.

The present position with regard to the major cardiac glycosides are shown below in tabular form.

Purgative Drugs

Senna—The general principles applied by Stoll to the isolation of the cardiac glycosides were also used in the isolation of the two active glycosides of *Cassia angustifolia*, i.e., senna, obtained from Tinnevelly, India. Stoll, Kussmaul and Becker published their findings in 1941 and announced the isolation of the Sennosides A and B, which represent the genuine pure laxative principles of the drug. The difference between the two glycosides lies in the linkage of the glucose and the various hydroxyl groups to the aglucone. These glycosides were introduced into medicine in the form of *Glysennid tablets*.

Conclusion

In recognition of his contributions to pharmaceutical chemistry, Prof. Stoll was honoured in 1935 with the Degree of M.D. by the Faculty of Medicine of the University of Basle. In 1936, he was invited by the College of the Pharmaceutical Society of Great Britain to deliver a course of lectures on "Cardiac Glycosides" which has since been published as a monograph. A degree of Doctor of Pharmacy was conferred on him in 1942 by the University of Berne. In 1943, Prof. Stoll received the Flueckiger Gold Medal from the Swiss Pharmacists Association. In the same year, the Marcel-Benoist Prize was given to Prof. Stoll, the highest award for scientific achievements in Switzerland. In December, 1945, Prof. Stoll received another Doctorate Degree from the Sorbonne University in Paris. He is undoubtedly one of the most outstanding continental personalities in the field of pharmaceutical chemistry and though nearing 60 years, is as active as ever. Fame and financial success have not changed his research outlook which he imbibed in his early life from his great teacher, Prof. Willstaetter.

The achievements of Prof. Stoll in the field of pharmaceutical chemistry stands as a monument of years of devoted and enthusiastic work. The training received under Prof. Willstaetter stood him in good stead and the 'team work', developed in his professor's (Willstaetter) laboratories, made such deep impression on Professor Stoll's mind that he succeeded in creating a 'school' of research workers in Switzerland. The importance of combining pharmaceutical chemistry with pharmacology and clinical work is nowhere more evident than in the laboratories of Prof. Stoll, where he has a well-organised pharmacological laboratory under Prof. Rothlin, and full-time clinicians are always available to try out the drugs and active principles that he has so far elaborated. His work has not only opened a new chapter in the field of pharmaceutical chemistry but has also brought into therapy several new and potent principles, of which 'ergotamine',

(Concluded at foot of col. 2)

HOW TO IMPROVE THE INTRINSIC VALUE OF MEDICAL JOURNALS IN INDIA

P. S. GUPTE, M.B.B.S., CAPT. I.M.S. (LATE)
Nasik

There is a general complaint that medical journals in India are starving for want of high class scientific articles. A memorandum from one prominent journal remarks that the main defect in improving the value of the journal is "the lack of original contributions of high order from the medical profession especially in the teaching line and attached to big hospitals." It continues to say, "after all education of the profession is the primary consideration of a medical journal." Apart from the evident self-interest of the profession at large this question of producing high class contributions is very important if India has to play a prominent and leading part in the field of medical science. It, therefore, behoves us all to pay closest attention to this ever-important problem.

History tells us that before the advent of Western influence there was a paucity of all scientific activities in India for at least two thousand years owing to absence of progressive and creative education. The country as a whole was a scene of wars and strifes and the people were too much absorbed in philosophic and spiritual subjects which we know are always at variance with the scientific mental attitude. Abstract philosophical mind cannot be expected to deal with the factual scientific matter. It is only recently from the middle of the 19th century that India is awakening from its torpor and apathy towards material sciences. Even now many of our universities are only examining bodies and are incapable of creating that spirit and thirst for knowledge amongst its alumni which is

(Concluded from col. 1)

'bellafoline' and 'digilanid' are important examples. It is yet early to forecast the future of his new dehydrogenated synthetic ergot alkaloids, but there is every possibility that these would constitute another valuable addition to the armamentarium of the physicians. In 'methyl ergobasine', which is about 1·3 times stronger than ergometrine, we are going to have an uterine stimulant stronger than the one available in the natural ergot, and in 'dihydroergotamine', there is a possibility of getting a sympathicolytic agent which might be superior to ergotamine, already in general use by the clinicians. Stoll has succeeded in a most difficult field of pharmaceutical chemistry which is concerned with the elaboration of active principles from natural drugs. In India, where we have a very large indigenous Materia Medica and where there will always remain the need for work on vegetable drugs, the example of Stoll would serve as a beacon-light to other workers. The chemistry of plant products owes a great deal to Prof. Stoll and therapeutics is richer to-day through his contributions in this field.

N.B. Most of the publications by Stoll and his co-workers are to be found in *Helvetica Chimica Acta*, and in *Sweizerische Medizinische Wochenschrift*. A useful reference in English is Stoll. A.—Cardiac Glycosides, 1937. Pharmaceutical Press, London.

essential to carry on laborious scientific research and to add new facts to the ever widening field of medical science.

Sources of medical literature can be divided into three classes:—(1) Research workers; (2) teaching and hospital staff and (3) medical practitioners working nation-wide amongst the people. Research workers include men who work in laboratories and do other scientific research which is more of a technical and academic nature. Their work is the real fountain of knowledge for the furtherance of medical science. Most of them in India work in Government-controlled institutions and contribute to their special journals which receive sufficiently high class scientific articles to fulfil their own needs. In my opinion these workers can condescend to write interesting and instructive articles for other medical journals in a simple and lucid manner on the problems in which they work. They will thus not find themselves cut off from the general medical profession for which ultimately they are undergoing so much labour.

We shall now discuss the second and third sources from which we expect articles to feed the journals dealing with the subject matter having direct interest to the teaching and hospital staff and general medical practitioners. We have every right to ask professors and other members of the teaching staff, physicians and surgeons of institutions to record their experiences and knowledge for the benefit of their professional brethren. We know there are many highly respected teachers who do not hold these posts for mere personal gains. They are the men who are supposed to be imbued with devotion to medical science and with a keen desire to spread the true spirit of education amongst students and medical practitioners. They should possess that compelling impulse to write which alone can build up the magnificent structure of medical literature. It should be an obligatory condition in selecting candidates that men with an aptitude for making original contributions are appointed to high posts of teaching and hospital staff. There should be a long apprenticeship before members are promoted to responsible posts. It is the people inspired with scientific mental attitude and endowed with the gift of writing who can produce useful and classical literature and kindle a spark in the hearts of young men to carry on the burning torch. That India has to depend on foreign nations for medical books and medical literature is simply heart-rending and ignominious.

To improve the present state of affairs of medical journals we appeal to the third source *i.e.*, the medical practitioners—who include specialists as well—to take more interest in the matters connected with medical science and medico-social problems. If true spirit of knowledge is created by the real masters of science who will be at the helm of teaching institutions and hospitals we shall have men in the profession inspired with a keen desire to contribute to medical literature from their practical experience in their daily work. Local medical associations can start manuscript magazines in their own circles and thus collect local contributions which can be forwarded to regular journals for publication. In this way local talents will be aroused by enthusiastic office-bearers of local societies to put up their experiences and knowledge before the medical profession. There will be thus no waste of clinical material which is so abundant in a vast country like India. Every medical man should remember the well-known dictum of Sir Thomas Browne that no one should enter the temple of science with the soul of a money-changer. It is not difficult to keep a day to day record of important medical experiences in one's practice if one has a will to do so. After some years it will be surprising to find what tremendous amount of subject-matter one possesses and on which one can draw to prepare informative articles of high order for publication. The source of high class scientific literature lies in the quality of work carried on in various fields of medical science by its members. Is it not our duty to discharge the debt of gratitude we owe to our predecessors who have left such a fine legacy for our use?

The local associations, clubs and unions should try to keep up living interest of their members in medical subjects by holding regular clinical meetings, by establishing study circles, by holding reading classes and by keeping libraries. In reading classes members should be asked to read select articles from journals of their own choice for the information of members. All doctors cannot be expected to read all journals from beginning to end. By conducting these activities on sound basis members will be kept informed of recent advances in different subjects and will have nice brain-dusting.

The problem of keeping libraries is very important. In the mofussil towns writer encounters great difficulty for lack of a good medical library for reference. Here either the doctor has to furnish his library at his own expense or forego the pleasure of reading books and sit quiet. Unless the associations take the initiative the town doctors have to live on old scraps of books or on occasional purchases he can make with his modest income. In this respect co-operative spirit is essential to keep up a well-furnished library of current useful books for practising doctors. A doctor without a library is like a ship without a compass. A single-handed person with his town practice cannot be expected to buy costly new editions of books in different subjects every year. And unless the local associations try to keep up libraries of modest size according to their means well-informed contributions from mofussil doctors can hardly be expected.

Journals themselves have also some responsibility to take active measures to induce people to write. They should offer substantial prizes and medals to those doctors who contribute the best articles and thus create healthy competition amongst the members. Journalism is a highly developed art and requires a well-trained staff to conduct it. Every journal should select and train candidates from the profession who wish to have journalism as their career in life. Scientific journals require a special class of people with high academic qualifications. Editors and sub-editors should be whole time servants and they must receive adequate remuneration commensurate with their high qualifications. They will then be keenly interested in conducting journals in an efficient manner.

CASE NOTES

A CASE OF OBSTRUCTIVE JAUNDICE DUE TO A PANCREATIC TUMOUR WITH AUTOPSY REPORT

KABIR HOSSAIN, M.B., D.T.M., F.S.M.F., KHAN SAHIB
Professor of Medical Jurisprudence, Medical College, Calcutta

One muslim male, aged about 45 years, who was suffering from vomiting and purging for 2 days, was removed to Medical College Hospital, Calcutta, by an ambulance on 6-10-45 and admitted therein at 10-15 A.M. He expired at 11 A.M. As the cause of death was not known, the dead body was sent to the Calcutta Police Morgue for post-mortem examination.

Post-Mortem Findings—This was a well-nourished subject. Pupils were dilated and equal, cyanosis was present in finger-nails. Marked jaundice was noticed all over the body. Decomposition already started.

On dissection of the dead body, the following conditions were observed:—

(1) Brain—Weighed 3 lbs. There was icteroid tinge in the brain and its membranes.

(2) Heart and blood vessels—Heart was markedly enlarged weighing 14 ounces. Both sides of the heart contained ante-mortem and post-mortem clots. There was atheromatous condition of the beginning of the aorta and right coronary artery was found sclerosed.

(3) Stomach—(8 oz.) was decomposed and contained a little mucoid fluid.

(4) Liver—(3 lbs. 14 ozs.) was markedly enlarged and gallbladder distended with thick bile.

(5) Spleen—(1 lb. 8 oz.) also markedly enlarged.

(6) Pancreas—A tumour of the size of a cricket ball was found in the head of the pancreas; yellow coloration of the peritoneum was also noticed.

(7) Other organs—Kidneys (6 oz. each), lungs, larynx and trachea were slightly decomposed, so also were small and large intestines—which contained mucoid stool.

Chemical Examiner's Report—No poison was detected in the stomach and its contents as well as in the liver and kidneys.

Discussion—The salient points for consideration in this case are as follows:—

(1) History of vomiting and diarrhœa.

(2) Post-mortem findings of the presence of a tumour about the size of a cricket-ball in the head of the pancreas as well as enlarged liver and spleen associated with marked jaundice all over the body.

(3) Enlarged heart with atheroma of aorta and sclerosis of right coronary artery.

But this condition of the heart and its blood-vessels without coronary thrombosis cannot account for death in this case; neither can it explain the symptoms of vomiting and diarrhœa in the living state nor marked generalised jaundice on autopsy.

On the other hand, marked jaundice with vomiting and diarrhœa can be easily explained by the presence of tumour in the head of the pancreas producing pressure on the common bile-duct. Post-mortem findings of markedly enlarged liver and distended gallbladder with thick bile were there as could be expected in a case like this.

The irritating products of bacterial decomposition of undigested fat and meat caused by deficient pancreatic digestion and lessened bile supply apparently gave rise to diarrhœa with excess of mucus in the stool; vomiting was also caused by the same factor.

Hence death in this case was, in my opinion, due to the effects of the tumour in the head of the pancreas and not due to cardio-vascular condition.*

*It is difficult to explain that the acute vomiting and purging were solely due to the pancreatic tumour—Ed., *J. Indian M. A.*

PULMONARY EMBOLISM SIMULATING CORONARY THROMBOSIS

K. S. MATHUR, M.B., B.S., M.R.C.P.,
Lecturer in Heart Diseases, Medical College, Agra

Pulmonary embolism was always considered to be a predominantly surgical post-operative complication. It is now more commonly met with in the practice of internal medicine, particularly in association with heart diseases. Levine and White (1937) recorded pulmonary embolism in 31 per cent of post-mortem on cases of mitral stenosis, whereas Kinsey and White (1940) found it in 48 per cent of autopsied cases of congestive heart failure.

The clinical manifestations of pulmonary embolism are so varied that the condition has been confused with many known clinical syndromes. Miller (1902) drew attention to the 'Significance of post-operative pleurisy in relation to pulmonary embolism'. Von Neusser (1909) recognised the pain simulating angina pectoris in association with pulmonary embolism. Conner (1914) described a 'Pulmonary attack simulating primary lobar pneumonia caused by pulmonary embolism complicating and simulating coronary thrombosis.'

Below is reported a case of pulmonary embolism with infarction closely simulating coronary thrombosis.

Case Report

O.P., 27 years, Hindu male, was admitted to the hospital on 23-3-46 with the complaint of pain in the præcordium and severe breathlessness, duration 2 days. The onset was sudden and unexpected while he was in bed.

Past history—He was admitted to the hospital on a previous occasion on 28-1-46 as a case of rheumatic mitral stenosis with congestive heart failure. The blood pressure was 114/70. Urine, stool, sputum examinations showed no abnormality. Blood examination showed slight anæmia, and W.R. was negative. Screen examination showed left auricular and right ventricular enlargements. He was put on complete rest in bed and digitalised. He was free from all symptoms at the time of discharge on 19-2-46, and was advised to continue the maintenance dose of digitalis which he did. His condition was very satisfactory when last seen on 19-3-46.

On examination—The patient was restless, extremely dyspnœic and in a state of severe shock. Respirations were shallow, laboured, 54 per minute. Cyanosis was very marked, sputum was blood tinged. Pulse rate was 140 per minute, low tensioned and thready. The extremities were cold and clammy. Temp. 99·4°F. Blood pressure 72/46 recorded at the time of admission. It fell to 62 systolic by the same evening and the diastolic could not be recorded.

Both lungs were full of moist rales and it was only in the evening that definite pleural friction rub was heard on the left side of chest, beyond the præcordial area. Heart sounds were heard with difficulty although the harsh presystolic murmur could be heard definitely in the mitral area.

Investigations—Blood: total white cells 21,000; polymorphonuclears 95 per cent, lymphocytes 5 per cent. X-ray of the chest on 27-3-46 showed an area of radio-opacity near the periphery of the middle zone of the left hemithorax.

Treatment and progress—Morphia gr. ¼ with atropine gr. 1/100, subcutaneously, glucose 25 per cent 50 c.c. with coramine 2 c.c. intravenously, and continous oxygen were given at the time of admission. Injections of coramine subcutaneously were given every 4 hours and injections of intravenous glucose every 8 hours. There was no improvement in his condition by the evening and it was decided to give him intramuscular injections of Sodium Dagenan every 4 hours in addition to coramine, glucose and oxygen. The following day *i.e.*, on 24-3-46, his condition was definitely better. The temperature was 98·4°F. pulse 100, respiration 34 and blood pressure raised to 92/68. Icteric tinge was noticed, pleuritic rub was still present, total white cells 19,000, polymorphs 90 per cent, lymphocytes 10 per cent. He was given in all 7 injections of Sodium Dagenan, glucose injections were continued twice daily. He made a steady improvement. On 28-3-46 the temperature was 97·6°, pulse 86, respiration 24, blood pressure 104/70, icteric tinge was still present, pleuritic rub had disappeared. Total white cells 12,750, polymorphs 91 per cent, lymphocytes 9 per cent. On 1-4-46 he felt so well that he walked a few steps out of the bed when nursing staff and nursing orderlies were away. The same night he suddenly got another attack of extreme dyspnœa, cyanosis and collapse similar to the one on the previous occasion although he did not speak and complain of any pain. His pulse was thready and imperceptible, blood pressure fell to 62 systolic, total white cells 25,000, polymorphs 91 per cent, lymphocytes 9 per cent. Inspite of all treatment he died within three hours of this attack.

Discussion—The sudden onset of præcordial pain, dyspnœa, shock, fall of blood pressure, rise in temperature and leucocytosis present a typical picture of coronary thrombosis. The young age of the patient, history of rheumatic mitral stenosis with congestive heart failure, cyanosis and tachycardia out of all proportion to evidence of heart failure, hæmoptysis, pleural friction rub, icteric tinge, the x-ray picture and the recurrence on the eleventh day left no doubt about the diagnosis of pulmonary embolism with infarction of the lung. Such a high leucocytosis is rare but not unknown in the condition. The response to Sodium Dagenan is surprising and cannot be explained except on the basis of septic embolus.

Summary—A case of pulmonary embolism with infarction of the lung simulating coronary thrombosis is described.

Acknowledgment—My thanks are due to Major-General H. C. Buckley, M.D., F.R.C.S., C.S.I., I.M.S., Principal, Medical College Agra, for his kind permission to publish the report of this case.

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PENICILLIN IN VENEREAL ARTHRITIS

N. C. DAS GUPTA, M.B.,
Khulna

Indian male, aged 35. Long history of gonorrhœal urethritis, for which he had various treatments beginning with Santal Midy and ending in sulphapyridine.

For over three months he had been suffering from arthritis of a number of joints and had taken more than a hundred tablets of M & B 693, milk injections, gonorrhœa phylacogen and vaccine without any effect.

When he consulted me the following joints were affected—both the temporo-mandibular, and the sterno-clavicular, the left later one with extensive inflammation all round it, the right shoulder and wrist with periostitis of the lower end of the radius, the left shoulder, the left sacro-iliac, both the knees, the left ankle and back of the right heel. He had been running a temperature; the spleen was enlarged one inch beyond the costal margin; constipated.

He denied the occurrence of any chancre or skin lesion.

Urethral smear showed gonococcus. Kahn test —strongly positive.

He was given penicillin 20,000 units intramuscularly every three hours upto a total of 2 lacs. Within a week all the joints became normal. The lesion of the radius and the os calcis refused to yield to treatment. Urethral smear on prostatic massage did not show any gonococcus.

He was now given acetylarson 3 c.c. twice a week and potassium iodide by mouth. After two injections the trouble completely disappeared.

It is impossible to say how much of the joint troubles were due to Treponema pallidum; probably it was entirely gonococcal readily responding to penicillin. The affection of the os calcis and the radius was certainly syphilitic periostitis on which at least two hundred thousand units of penicillin had no action, but which promptly yielded to arsenic.

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THE NATIONAL HEALTH SERVICE BILL AND THE BRITISH MEDICAL ASSOCIATION

We have watched with great interest the controversy between the British Medical Association and the Labour Government in the United Kingdom regarding the National Health Service Bill. A general description of the proposed health service was issued as a Government White Paper.[1] At the time of writing this comment the bill is in the Committee stage where every clause is being discussed. The bill plans for a comprehensive health service and as such provides for the following kinds of health services:—(*i*) Hospital and specialist services, (*ii*) health centres and general practitioner services, (*iii*) various supplementary services, and (*iv*) the provision of spectacles, dentures and other appliances, together with drugs and medicines. Generally speaking the bill aims at a personal health service by the doctors and dentists, whom the patient chooses, either at health centres, at home or at the doctor's office. The service will be available to all, free and without qualification or limitation. Doctors may choose whether or not to join the services, and joining it will not debar them to accept fees from those patients who do not want to take advantage of the State scheme. All forms of general and specialist hospital care and treatment are included under this scheme. These again, will be available at hospitals, institutions, clinics and in the patient's home. The Minister-in-charge will take over public and voluntary hospitals. He will be responsible for the service and this will be administered by regional boards. Local Health authorities will administer the supplementary services which will include midwifery, maternity and child-welfare, home nursing, a priority dental service for children and expectant and nursing mothers, and domestic help when needed on health grounds. Each doctor will have his own list of patients whom he has agreed to attend. The patient's freedom to choose his own doctor is not cancelled nor will there be a general direction for doctors. But the movement of doctors will be restricted within the national health service. Payment of doctors will be partly by salary and partly by capitation fee. The sale of practices in the health service will be totally prohibited and compensation will be paid to present practitioners for loss of selling values. For areas which are unattractive and short of doctors, the salary will be adjusted to induce them to practise in those areas. In his speech on April, 30, Mr. Aneurin Bevan, Minister of Health, explained the distribution of doctors, in moving the second reading of the Bill in the House of Commons.[2] He said that some doctors claimed that the scheme meant direction but no direction was really involved. All the doctors in an area would be entitled to enter the public service in that area. A new doctor's application to set up in practice in an area would be referred to the Medical Practices Committee, a mainly professional body and if it were held that already there were sufficient doctors there, the application would be refused. By negative control over the number of doctors they hoped to bring about a positive control over the medical services all over the country. A new doctor would have to find his practice in a place inadequately served.

The British Medical Association (B.M.A.) rightly points out that the medical profession has stressed the need for a complete health service for the last 25 years or more. It offered its co-operation in evolving a scheme for service and enunciated the following principles as drawn up by the negotiating Committee as a basis for helpful discussion with the Government[3]:

(*i*) The medical profession is, in the public interest, opposed to any form of service which leads directly or indirectly to the profession as a whole becoming full time salaried servants of the State or local authorities.

(*ii*) The medical profession should remain free to exercise art and science of medicine according to its traditions, standards and knowledge, the individual doctor retaining full responsibility for the care of the patient and freedom of judgment, action, speech and publication, without interference in his professional work.

(*iii*) The citizen should be free to choose or change his or her family doctor, to choose, in consultation with his family doctor, the hospital at which he should be treated and free to decide whether he avails himself of the public service or obtains independently the medical service he needs.

(*iv*) Doctors should, like other workers, be free to choose the form, place and type of work they prefer without Governmental or other direction.

(*v*) Every registered medical practitioner should be entitled as a right to participate in the public service.

(*vi*) The hospital service should be planned over natural hospital areas centred on universities in order that these centres of education and research may influence the whole service.

(*vii*) There should be adequate representation of the medical profession on all administrative bodies associated with the new service in order that doctors may make their contribution to the efficiency of the service.

The *British Medical Journal*[4,5,6,7,8,9] in its various leading articles explained the position of the medical profession with regard to the Bill. It praised the proposal in the bill for organisation of hospitals

[1] *Brit. M. J.*, **1**:461, 1946.

[2] *Lancet*, **1**:701, 1946.
[3] *Brit. M. J.*, **2**:833, 1945.
[4] *Ibid.*, **2**:851, 1945.
[5] *Ibid.*, **1**:489, 1946.
[6] *Ibid.*, **1**:575, 1946.
[7] *Ibid.*, **1**:612, 1946.
[8] *Ibid.*, **1**:686, 1946.
[9] *Ibid.*, **1**:725, 1946.

on a regional basis. But taking away of all the hospitals by the State may cause a loss of public interest and contribution. The Journal argued that the bill should be considered first by the public interest and second by the principles which had guided the profession to the formulation of the policy. Beneath these principles it can be seen that there was a firm determination to convert the profession into another technical branch of the Government. As such there is a danger to divide the loyalty of the doctor between his patient and the State—which employed and directed him. The Bill does not contain any proposition for a wholetime salaried service under the State at present, but it contains the germ of such a service. It is pointed out that in the interest of the patient, the doctor should be absolutely free within his field. The way in which a 'doctor's certificate' has been, criticized by the employers, it is feared that the State may develop an urge to cut short illnesses, save funds and man power. The other danger in its extreme is described in a letter from a patient.[10]

"Heaven knows what will happen to the sick and injured when the medical service of the whole country has become part of the state machine? There will be no court of appeal for the casualties of war and industry. Treasury officials will be free to squeeze those of the Ministries of Health and National Health Insurance, who themselves, to obtain the economies demanded, will exert their pressure upon doctors. After the medical profession has been 'nationalised' from whence will it be possible to obtain the services of a free and independent doctor."

"With the services the 'yes-man' will go to the top, not the pioneer exploring the mysteries of science and probing the imponderables of human nature. The 'Smart Alecks', the form fillers, and busy bodies and chatterboxes will run after the well-paid easy posts behind the desks. These will run up the ladder of promotion while the skilled surgeons and physicians do the hand work in the 'field'. We shall have the 'brass hat' at headquarters and the 'troops' fighting disease in the lines. This system may work well for an Army fighting Germans or Italians, but has it ever served any useful purpose elsewhere ?"

On April 4, 1946 at a London mass meeting of practitioners, Dr. Charles Hill, Secretary of the B.M.A., brought out the following points[11]:—

"Those who maintain that our profession is obstructive and stands in the way of a better health service either do not know the facts or are wilfully misrepresenting them for their own purposes."

"It is wrong to say our opposition is unqualified. The Bill is an amalgam of good and bad. For example, the proposed hospital service is an imaginative scheme, which in its regional aspects will meet with the approval of the profession as a whole."

"But it is unnecessary for the Minister to proceed to actual ownership of hospitals. All the power he requires is his by virtue of control of the purse. If a hospital is to hold its rightful place in the community and remain a centre of local pride and affection it should be locally owned and not become a State establishment."

"To divide the loyalty of the family doctor between the patient and some superior and appointing body is not in the public interest."

"We must examine the proposals in relation to principles and not to compensation or remuneration."

"Let us remember that no government can bring into being any health service without the co-operation of the profession. That is not a threat. It is my business to state the facts that we must bear in mind."

The *Journal of the American Medical Association*[12] thinks that Britain's National Health Act is one of the most backward steps ever conceived for a civilised nation. It draws attention to the fact that doctors without being reduced to the status of subservient mechanics, have contributed to this tremendous advance in scientific medicine. Even during the period of war, the contribution of the independent medical men in the field of antibiotic drugs, of blood derivatives, of new surgical techniques, of control over insect-borne diseases, has increased life expectancy and in the face of this constant advancement, the politicians should promote a revolution in methods of medical education, medical research and medical care, unthinking of any steps that may "destroy the scientific medical forces that have yielded these results."

As envisaged in the Patna resolution of the I.M.A.[13] there is hardly any body who appreciates more than the medical profession that medical care should reach every person. Expenses should not be a barrier in this service to humanity. At the same time it must never be forgotten that to make it a success and effective in its proper perspective, the loyalty of the doctor towards his patient should not be curtailed or influenced by red tape. As Sir Lionel Whitby has said, "One of the attractions of the profession is the personal and individual character of its practice: the latitude with which a qualified doctor may exercise his own judgment, express his own opinions and practise his own art." Whether the free medical aid to suffering humanity is given through service or otherwise, for the best interest of the patients and doctors alike, the profession must remain independent and free from the influence of the government bureaucracy. No health service should be forced on the profession merely by passing it through the House of Commons. Mutual co-operation and understanding can only produce a formula best suited for the sick. The history of scientific medicine is studded with the wonderful achievements of the British medical profession which have earned universal respect. We hope some scheme will be evolved which will retain this brilliant tradition.

[10] *Brit. M. J.*, Supplement: **1**:46, 1946.
[11] *Ibid.*, **1**: 580, 1946.
[12] *J.A.M.A.*, **130**:859, 1946.
[13] *J. Indian M. A.*, **12**:239, 1943.

CURRENT MEDICAL LITERATURE

Dengue Group of Fevers in India

Karamchandani (*Lancet*, **1**:92, 1946) believes that the 5-day fever of Scheer and 7-day fever of Rogers are examples of the same disease. The grouping together of those fevers would focus medical attention on sporadic mild forms of fever which at present are diagnosed either as clinical malaria or as influenza. The question of sandfly fever is more debatable, but there are certain clinical and aetiological similarities between this and the dengue group. Both diseases are transmitted by an insect, the infection being caused by a filtrable virus in the blood-stream. Both are diseases of warm climates and clinically have a short incubation period and a brief rapidly developed fever associated with a slow pulse, leucopenia, and relative decrease of polymorphonuclear cells. The viruses of dengue and sandfly fever have much in common. The main features of the "dengue group of fevers" would be as follows:

(1) Sudden and abrupt onset, with generalised pains and no local manifestations of an acute inflammatory condition, such as tonsillitis or a septic infection.

(2) Absence of parasites in the blood and absence of leucocytosis rather a tendency to progressive leucopenia.

(3) Fever with a short self-limited course, the temperature being (*a*) of the saddle back type, either continuous (average duration 5 days) or interrupted (average duration 5 days); (*b*) continued (average duration 7 days); (*c*) of the short one-phase type (average duration 3 days); or (*d*) of the larval type (average duration less than a day).

Varieties in the disease are due to differences either in the strains of the virus or in the susceptibility of the patient.

Nutritional Deficiency in Diabetes

Biskind and Schrier (*Exper. Med. & Surg.*, **3**:299, 1945, Ref. *J.A.M.A.*, **130**:535, 1946) believe that diabetes mellitus represents in the vast majority of patients impairment of hepatic response to endogenous insulin and that this results from protracted vitamin B complex deficiency. Thus the concept of insulin resistance may be extended to include most patients with diabetes. Among 94 diabetic patients studied, every one showed signs and symptoms of deficiency of factors of the B complex. Intensive and persistent oral or oral and parenteral therapy with vitamin B complex led to striking improvement in general health and often to great improvement in carbohydrate metabolism, frequently with reduction in insulin requirement or its elimination altogether.

Hypoglycaemic Fatigue

Karlan and Cohn (*J.A.M.A.*, **130**:553, 1946) believe that hypoglycæmic fatigue is a definite syndrome consisting of fatigue and dizziness after periods of abstinence from food or after exercise. There are other vague symptoms of varying degree. The syndrome can also be reproduced by the administration of insulin. The laboratory tests show glucose tolerance curves which are flat or in the course of which the true blood sugar falls to below 50. If the patient is properly prepared and true blood sugars are estimated, the blood sugar is of definite significance. This does not mean that every patient with a flat curve or low blood sugar experiences this symptom complex. However, the authors believe that patients with the complaints described who have flat curves have hypoglycæmic fatigue. The necessary criteria can be demonstrated in only a small percentage of patients with fatigue. It is important to differentiate hypoglycæmia from neurasthenia in order to institute proper therapy. Atropine had no significant effect on either the results of the glucose tolerance tests or on the symptoms. The authors therefore, do not concur in the theory that the condition is due to excessive stimulation of the vagus nerve. They examined the patients psychiatrically and could find no definite relationship between the emotional state and the degree of hypoglycæmia. They conclude:

1. In 9 cases of fatigue and dizziness due to hypoglycæmia the hypoglycæmia was demonstrated by the intravenous glucose tolerance test and true blood sugar determination.
2. Dietary treatment (high proteins and complex carbohydrates) with frequent feedings was effective in alleviating the symptoms.
3. No causal relationship between the hypoglycæmia and the emotional status could be found.
4. Atropine had no beneficial effect on the hypoglycemia or on the symptoms.
5. All cases of neurasthenia and fatigue should be investigated for hypoglycæmia.

Rheumatic Brain Disease

It is common knowledge that rheumatic fever may involve the central nervous system, Sydenham's chorea being the best-known example. Recent research carried out in the United States suggests, however, that the incidence of lesions in the brains of patients with a history of rheumatic fever is far greater than has been realized before. In a review of his work Bruetsch (*Arch. Int. Med.*, **73**:472, 1944) has pointed out that in only one of thirty patients who had rheumatic valvulitis was the brain free from changes. These changes consisted of obliterating endarteritis of the small meningeal and cortical vessels with subsequent gross or microscopical softenings in the cerebral cortex. They are clearly distinguished from cerebral embolism occurring in patients with mitral stenosis during auricular fibrillation. Involvement of the brain may arise many years after the acute stage of rheumatic fever. The possibility that these lesions may give rise to mental symptoms led Bruetsch to study a group of 500 consecutive necropsies in a mental hospital. He found evidence of rheumatic heart disease in 5%, as compared with an estimated figure of less than 1% for the general population. Among schizophrenics the incidence was as high as 9%. Bruetsch discusses a possible causal relation between rheumatic fever and various types of mental disease, but it is clearly desirable that any such conclusion should be deferred until more statistical evidence is available. Even if further work should confirm the results obtained by Bruetsch, the relation between schizophrenia and rheumatic disease might well prove to be of a concomitant nature, not unlike that of tuberculosis, which is also said to be relatively frequent in schizophrenics.

It has been stressed by Bruetsch and others that the vascular changes in the brain are not pathognomonic of rheumatism, but may also be found in other conditions—for example, bacterial endocarditis. It remains to be seen whether recent work on allergy may throw light upon the pathogenesis of the lesions, which are not unlike those described in anaphylactic experiments after protracted sensitization (Ferraro—*J. Neuropathol. exp. Neurol.*, **4**:1, 1945). This would place the rheumatic lesions in line with periarteritis nodosa, for there is now strong experimental (Reich and Gregory—*Johns Hopk. Hosp. Bull.*, **72**:65, 1943) and pathological (Miller—

Lancet, **2**:200, 1945) evidence that this condition is an allergic reaction, and, perhaps, also with thrombo-angiitis obliterans. Both conditions are now assuming some neuropathological importance, as they appear to affect the brain more often than was previously known (SCHEINKER—*Neuropathol. exp. Neurol.*, **4**:88, 1945).

EFFECT OF VITAMIN E ON IMPAIRED KIDNEY FUNCTION

SHUTE (*Canadian M. A. J.*, **52**:151, 1945) reports the results of the administration of vitamin E (ephynal-synthetic α-tocopherol) to thirteen women suffering either from chronic nephritis or impaired renal function, such as chronic œdema not of cardiac origin, or hypertension. Some of the cases were post-puerperal, the pregnancy having been complicated by toxæmia. As a rule, two separate tests for kidney function were made before the institution of treatment, which consisted of the administration of 25 mgm. ephynal daily, for two weeks. At the end of this time the two-hour test was repeated in order to assess improvement. Benefit was obtained in ten of the thirteen cases treated; the improvement developed quickly but was transient unless therapy was continued, and, in most cases, it was limited to the tubular system of the kidney. In addition to the cases referred to above, a man of forty-three, with a blood pressure of 180/100 mm. Hg., severe albuminuria and œdema, was given one tablespoonful of Kelly's wheat germ oil per day. After seventeen days of this treatment the albuminuria was halved and the blood pressure was 150/80 mm. Hg. Two months later the blood pressure had fallen to 137/75 mm. Hg., the edema had disappeared, and there was a decrease in weight. Three months later the wheat germ oil was reduced to one dessertspoonful daily. The improvement continued, and nine months later, *i.e.*, fifteen months after the institution of treatment, the vitamin-E therapy was discontinued. One year later the albuminuria was one plus, and five months later there was only a faint trace of albumin present. The author states that the results obtained in this case may indicate a role for vitamin-E therapy in the treatment of nephrosis.

INDIVIDUAL VARIATIONS IN THE ABSORPTION OF DRUGS FROM THE INTESTINAL TRACT

CHOPRA AND CHOPRA (*Miscellany*, **13**:67, 1946) in dealing with the subject write that the practitioner in tropical and subtropical climates would bear these in mind:—

The absorption of drugs is considerably modified in acute and chronic inflammatory conditions of the mucous membrane of the gut.

The hypoacidity of the stomach which is often met with in chronic dysenteric and other infections has considerable effect over the absorption of drugs.

The rapid passage of meals through the small intestine generally and through its upper part particularly where these drugs are usually absorbed, hinders absorption. This is quite commonly met with in amœbic and bacterial dysenteries and affections of the liver.

The drugs administered in form of tablets may not be properly constituted. Some of the ingredients used may prevent their disintegration before reaching the part where absorption of drugs takes place. In some cases the tablets may not disintegrate at all, and may pass through the gut unchanged.

PROLONGED ADMINISTRATION OF QUINACRINE

MAEGRAITH (*Ann. Trop. Med.*, **39**:128, 1945) writes that the experimental subjects were 43 healthy men, Oxford undergraduates and soldier volunteers who had not taken quinacrine previously. Approximately 0·1 gm. of quinacrine daily was given over a period of nine to twelve months. Tests of liver and kidney function were made and compared with tests done before the administration of quinacrine. Evidence indicated that this course of quinacrine did not impair the efficiency of the liver or the kidney.

FOLIC ACID IN MACROCYTIC ANAEMIA IN RELAPSE

SPIES (*J.A.M.A.*, **130**:475, 1946) observes that synthetic folic acid administered either parenterally or orally is effective in producing a significant hæmopoietic response in persons with nutritional macrocytic anæmia, or with the macrocytic anæmias of pellagra, of pernicious anæmia, of sprue or of pregnancy. This hæmopoietic response is characterized by an increase in reticulocytes, red blood cells, white blood cells, platelets, normoblasts and hæmoglobin. The megaloblasts in the bone marrow are decreased following therapy.

It is worthy of emphasis that none of the patients with aplastic anæmia, iron deficiency anæmia or the anæmia associated with leukæmia showed any improvement. We have found that folic acid corrects the leukopenia of certain nutritional condition but does not correct the leukopenia of a number of infectious diseases or idiopathic states.

The subjective and the objective improvement which follows the administration of folic acid to persons with macrocytic anæmia in relapse is similar to that which follows liver extract therapy.

The exact minimal and optimal doses of folic acid have not been determined, but these studies indicate that there is some variation from patient to patient. Although the authors have found that the administration of as much as 400 mg. daily has not caused any untoward symptoms, a daily dosage of from 5 to 10 mg. parenterally or some 10 mg. by mouth will often produce a maximum hæmopoietic response. In order to determine the optimal and the average doses, the study of many more patients will be required.

Two additional patients have been studied with macrocytic anæmia who have developed such severe sensitivity to various forms of liver extract that they were unable to tolerate injections in sufficient amounts to maitnain proper blood values. In both cases folic acid was substituted for the liver extract safely and satisfactorily.

Folic acid (synthetic Lactobacillus casei factor), a vitamin present in liver, yeast and other food materials, is a potent antianæmic factor in certain types of macrocytic anæmia in relapse. Folic acid performs a specific function in the maturation of the various cells of the bone marrow and has other obvious profound effects on our bodies.

PENICILLIN IN AGRANULOCYTOSIS

BOLAND AND OTHERS (*J.A.M.A.*, **130**:559, 1946) write that sulphonamides and penicillin have been used in the treatment of granulocytopenia or agranulocytosis. At first they were used more often despite the presence of agranulocytosis rather than specifically for it. Seven cases of agranulocytosis successfully treated with sulphonamides have been reported. But because sulphonamide may themselves produce agranulocytosis, penicillin would seem to be the remedy of choice.

Ten cases of agranulocytosis, including the 1 here reported, have now been treated with penicillin: prompt recovery has occurred in every case. This represents a notable improvement in the treatment of the condition and allows for much greater optimism in prognosis than has heretofore been possible. In some of these 10 cases leukopoietic agents were used in conjunction with penicillin alone. Experiences to date indicate that penicillin constitutes the most potent remedy at hand for the prevention or control of the serious, potentially fatal complication of agranulocytosis.

Benadryl in Urticaria

Curtis and Owens (*Arch. Dermat. & Syphil.*, **52**:605, 1945) write that benadryl (beta dimethylaminoethyl benzhydryl ether hydrochloride) is a member of a new group of pharmacologically active antihistamine drugs. They administered it in amounts of 50 to 100 mg. orally one to five times daily to a diverse group of 18 patients with both acute and chronic urticaria. Eleven patients experienced prompt relief of symptoms as long as the drug was taken. Three had definite and real improvement, and many of the wheals which did appear were not pruritic. Four patients were not benefited. The drug has a wide margin of safety. The only toxic manifestations noted were drowsiness and muscular aching (2 cases), dizziness, weakness and vertigo (1 case). Cumulative toxic symptoms were not noted in patients who ingested the drug as long as six or seven months. All toxic symptoms promptly disappeared when the drug was discontinued. The effect is palliative, and in many patients the urticaria recurred when the administration of the drug was discontinued. Since an antihistamine drug seems to be effective in controlling urticaria, it may be assumed that this is further indirect evidence that histamine is a factor in the production of urticaria.

Diethylstilbestrol Treatment of Haemophilia

Chassagne (*Progres. Med.*, **73**:282, 1945, Ref. *J.A.M.A.*, **130**:542, 1946) writes that intramuscular injections of 0·5 to 1·0 mg. of diethylstilbestrol in oil every day for five days were effective in restoring the coagulation time to approximately normal levels. The same effect may be produced by the oral administration of a 5 mg. tablet three times a week. The author suggests large doses of the drug during hæmorrhagic periods. Five to 10 mg. should be administered by mouth every day for one week, or 1 to 5 mg. should be given intramuscularly every day during this period. Several days are required to obtain an improvement in the coagulation time. Apart from the hæmorrhagic periods, a prolonged treatment is required. This should consist of oral administration of 1 to 3 mg. of the drug every day or every second day for several weeks. Pigmentation of the genitals following administration of the drug was observed in adults and in adolescents.

A New Treatment of Lupus Vulgaris

Dowhing and Thomas (*J.A.M.A.*, **130**:527, 1946) at the section of dermatology of the Royal Society of Medicine reported remarkable results from the treatment of lupus vulgaris with large doses of calciferol. They had treated 38 cases, of which 16 have been followed for more than a year. In all improvement was observed and in 12, lesions seem to have disappeared entirely. In 1 there has been no return of the disease in the eighteen months since the treatment was stopped. A few have shown little benefit, but the majority have been strikingly improved after making poor progress under other treatment. The dermatologists who saw some of the cases were much impressed. This new treatment is far simpler and much less expensive in time and effort than current methods, such as frequent exposures to Finsen light or ultraviolet rays. But the treatment has the disadvantage of requiring doses which border on the toxic. At least 8 patients have shown signs of intolerance, such as nausea, loss of appetite and depression. Most of these received 150,000 international units of calciferol daily. In all of these the toxic symptoms disappeared when the dosage was reduced to 100,000. Unlike the natural vitamin D obtained from fish liver oils, calciferol is prepared artificially by irradiation of a vegetable sterol, ergosterol, and the preparations may include toxic by-products of irradiation. Very large doses are known to cause deposition of calcium in soft tissues, notably the renal tubules and arterioles and the media of large blood vessels. Though this calcification tends to disappear on discontinuance of the calciferol, it should not be used on the scale employed by Dowling and Thomas without careful consideration of the case and watching for toxic symptoms.

New Treatment of Amoebiasis

Sokoloff (*Rev. Gastroenterol.*, **12**:425, 1945) found that lactic acid, even in a weak solution of 1:1,000, impedes the multiplication of protozoa, including amœbæ. Since ingested lactic acid is actively absorbed in the small intestine and therefore is of little use in the treatment of infections of the large intestine, a special anhydrous form of lactic acid, trilactic, was developed. Trilactic dissolves in water slowly and for this reason reaches the colon and cæcum without being affected greatly by the gastric juice. Research has demonstrated that trilactic has a therapeutic effect in animals infected with pathogenic bacteria. Rats infected with Entamœba histolytica were submitted to trilactic therapy. Although they had only a mild form of amœbiasis, their stools showed presence of trophozoites and cysts. These disappeared after seven days of treatment with trilactic. The animals seemed to have been completely cured. During the last five years trilactic has been tested on a number of patients with amœbic infection. In many instances they received the trilactic treatment after emetine had failed to eliminate completely the pathogenic amœba, or when the patient had experienced a toxic reaction from this drug. In a few instance trilactic was administered after protracted iodine therapy when stools still showed presence of the cysts. Such combined therapy showed the most satisfactory results not only in the complete elimination of the amœba but also in the prompt restoration of the normal bowel movement. Sixty-two patients affected with acute and chronic amœbic infections have been treated with trilactic. Complete recovery was obtained in 36, improvement in 15 and negative results in 11 patients.

Use and Abuse of Parenteral Fluids

Flink (*Minnesota Med.*, **29**:347, 1946) writes that valuable as the administration of parenteral fluid may be, one can err seriously in giving too much fluid containing electrolytes to patients who need only glucose in water or in not giving fluid containing electrolytes to patients who need them.

The normal adult drinks 1500 c.c. or more of liquid daily. In addition he obtains about 1200 c.c. of liquid from his food. The moisture lost through insensible perspiration and expired air amounts to about 1200 c.c. so that the liquid obtained from food balances approximately that lost from the skin and lungs.

The 1500 c.c. of liquid drunk during the day is necessary for proper kidney function in the elimination of salts and waste products of nitrogen metabolism. Fever, high environmental temperatures, and exertion even without sweating increase the loss from skin and lungs and consequently increase the fluid requirement.

If, for any reason, a normal amount of fluid cannot be taken by mouth, parenteral fluid is indicated. Following an operation for instance, when a patient is unable to eat or drink, he requires from 3000 to 4000 c.c. of parenteral fluid to prevent dehydration. All this should not be given in the form of physiological saline or lactate-Ringer's solution. Acutely ill patients and particularly postoperative surgical patients tolerate excess sodium chloride very poorly. Pulmonary œdema, peripheral œdema and oliguria can result from the use of too much saline solution in such patients. The normal daily intake of sodium chloride ranges from 4·0 to 10·0 gm. so the administration of saline parenterally should be limited to 4·5 gm. sodium chloride in each twenty-four hours unless there is an abnormal fluid loss by fistula, drainage, etc. It should be remembered that physiological saline solution contains 9·0 gm. of sodium chloride per litre and lactate-Ringer's solution contains 6·0 gm. of sodium chloride and 2·7 gm. of sodium lactate per litre. Three litres of saline solution contain 27·0 gm. of sodium chloride and the same volume of Ringer's solution contains 18·0 gm. of sodium chloride and 8·1 gm. of sodium lactate. It should be remembered that plasma, amino acid solutions and blood contain the chloride and other Na salts in appreciable amounts.

If gastric or duodenal suction has been instituted, there is need for additional parenteral fluid and sodium chloride to replace that lost through the suction. Fluids obtained from the stomach and duodenum contain approximately an equivalent of 5·0 gm. of sodium chloride per litre. Fluids and sodium chloride lost by suction should be replaced. Determination of plasma chloride levels at intervals is essential if suction is continued for many days, for the above replacement rule represents minimal requirements.

There are many conditions which cause dehydration by the excessive loss of both water and electrolytes: copious vomiting from pyloric obstruction, intestinal obstruction or other causes; severe diarrhœa; drainage from external biliary, pancreatic, and other fistulæ; transudation or exudation of fluid from large denuded or burned areas; profuse sweating; diabetic acidosis with loss of fixed base combined with acetone bodies; and excessive loss of sodium chloride in the urine of patients with Addison's disease. Serious errors can be made by failing to supply adequate sodium chloride (or sodium chloride with sodium lactate or bicarbonate) in the appropriate instances. Each of the above causes of dehydration represents a special problem and cannot be discussed here, but it must be emphasized that these conditions must be recognized and treated properly.

In medical cases it is just as important to preserve electrolyte balance. If the kidney function is impaired to such an extent that the blood urea nitrogen and creatinine are increased, water is needed in larger volume than in normal individuals for the elimination of metabolic products. If the plasma chloride is normal or elevated in the presence of edema, sodium chloride in the diet or saline solution parenterally is contraindicated. Parenteral fluid in the form of glucose in distilled water may be given. Schemm has shown that in the presence of œdema of nephritic or cardiac origin, fluid without salt and an acid ash diet will help reduce œdema by their diuretic action. Saline solution will only aggravate the œdema present and tend to produce pulmonary œdema. Water should not be restricted even in the presence of œdema but may be formed if the salt intake is restricted.

Value of Protein in Surgical Repair

Co Tui (*Bull. New York Acad. Med.*, **21**:631, 1945) stresses that proteins are essential to wound healing, the maintenance of tissue integrity and expeditious convalescence. Protein deficiency endangers all three. A patient can become protein deficient as a result of inadequate intake and increased nitrogen output or a combination of these two factors. Decreased intake may be due to the patient or to neglect on the part of the attending staff. Increased output may be due to increased metabolic loss and to the loss through exudates. The ceiling of nitrogen intake in natural food is naturally low, and consequently natural food is often inadequate to replenish the increased protein loss in disease and injury. Studies in cases of burns and of postoperative gastrectomy cholecystectomy and herniotomy suggest that convalescence can be shortened, strength and weight conserved by full caloric and nitrogen replacement immediately postoperatively and that there may be a critical range of nitrogen intake for each disease category. The protein hydrolysates are indispensable in many disease conditions and can be used with greater elasticity than natural food. In the course of study on the value of protein hydrolysates a new treatment of peptic ulcers has been evolved. Protein hydrolysates for clinical use must fulfil a number of criteria, and clinicians using them must be quantitatively minded. The nutritional status can be studied by (1) nitrogen balance, (2) plasma protein curve, (3) body weight curve and (4) bedside ergograph.

Tetanus in the European and African Campaigns

Boyd (*Lancet*, **1**:113, 1946) gives in the following words the summary of his observations.

The incidence of tetanus in the African and European campaigns has been negligible. This is chiefly attributable to active immunisation with tetanus toxoid.

Active immunisation did not prevent the development of tetanus in 22 cases.

The case-mortality rate among the actively immunised did not fall below the average, but it is noteworthy that the majority of fatal cases were in coloured troops.

The case-mortality rate in actively immunised men who were given prophylactic antitoxin was significantly lowered.

The duration of the symptoms in actively immunised men who survived was also significantly lowered.

The incubation period in the actively immunised rarely exceeded 10 days, whereas in most of those not immunised the incubation period was more than 10 days.

Failure of active immunisation appears to be attributable to an inadequate level of circulating antitoxin in the early stages of infection and is more likely to be remedied by prophylactic antitoxin than by a "booster" dose of toxoid.

Therapeutic antitoxin, to be effective, must be given as early as poossible in large doses by the intravenous route.

Sedatives, including avertin and pentothal did not influence the course of the disease, although they were effective in relieving symptoms.

Penicillin in Prevention of Prenatal Syphilis

Goodwin and Moor (*J.A.M.A.*, **130**:688, 1946) give in the following lines the summary of their observations:—

1. Fifty-seven pregnant women with early syphilis have been treated with penicillin in two university clinics. Sixty infants have been born to these women, all of whom were born alive; only 1 has developed clinical or laboratory evidence of congenital syphilis. In this 1 case, syphilis in the child might possibly have been prevented. The remaining 59 infants are all apparently normal, and 42 of these have been followed for a long enough time after birth to make practically certain of the diagnosis of "no syphilis."

2. These results in the prevention of prenatal syphilis are superior to any heretofore attainable with any method of treatment.

3. There is no satisfactory evidence that penicillin is directly or indirectly responsible for abortion.

4. It is recommended that in syphilitic pregnant women penicillin be used routinely for the prevention of prenatal syphilis, other methods of treatment being abandoned.

Penicillin in Syphilitic Pregnant Woman

Ingram and others (*J.A.M.A.*, **130**:683, 1946) write: (1) one syphilitic infant has occurred among 37 syphilitic pregnancies treated with penicillin, which have reached term. In 27 of these cases the infant has been followed for periods greater than two months postnatally and the presumptive evidence that the infant is normal is good. This represents a degree of success equal to if not greater than that obtained with the arsenical-bismuth regimens at present widely employed.

(2) Either 1·2 million or 2·4 million Oxford units total dosage seem satisfactory for the pregnant woman, though the larger dosage is preferred. It is recommended that the dosage be reduced to one fourth during the first twenty-four hours and to one half during the second twenty-four hours to reduce the possibility of threatened abortion from therapeutic shock and that the duration of treatment be prolonged to eight or nine days.

(3) The serologic response to penicillin treatment of the pregnant woman is apparently considerably slower than the average for early acquired syphilis in the adult. It is not necessary, on the other hand, that the mother be seronegative at the time of confinement in order for the infant to be normal.

(4) As a result of our continued use of penicillin in the treatment of the pregnant woman with early syphilis, we are confident that this drug represents a distinct advantage in that it is a convenient, safe and effective mode of therapy.

Basal Body Temperature and the Menstrual Cycle

It is now over forty years since Van der Velde described changes in the basal temperature of the body during the menstrual cycle. Since his original description in 1904 knowledge of the physiology and pathology of the endometrium has grown, and it is now possible to correlate fluctuations of body temperature with changes in the uterus and ovaries. Tomkins (*J. Obstet. & Gynæc. Brit. Emp.*, **52**:241, 1945) in a paper illustrated with numerous valuable graphs, shows that the curve of body temperature in the normal menstrual cycle is biphasic. Before ovulation the temperature is relatively low. Ovulation is signalled by a fall of temperature followed by a sharp rise to a higher level. Another sharp fall one to three days before menstruation brings the temperature down again to the relatively low level which persists until the next ovulation. If conception occurs the premenstrual fall is absent and the temperature remains at the higher level. In an earlier paper Tomkins (*J.A.M.A.*, **124**: 698, 1944) recommended that the temperature be taken by the rectum on waking in the morning, before rising, and before taking food and drink or smoking. The reading must be recorded at once on the special graph. Any indisposition, such as a cold or indigestion, should be noted even a "hang over" may vitiate the record. Coitus and mittelschmerz should also be noted. Records are not necessary during menstruation. The graph is not considered of value until it has been kept for at least two months; ovulation is indicated by a rise in basal body temperature of 0·4 to 0·6°F.

Commenting on this study, Kleitman (*J.A.M.A.*, **125**:92, 1944) suggests certain modifications. He finds oral temperatures as efficient as rectal provided precautions are taken, such as resting and avoiding hot drinks within an hour or cold drinks within half an hour of recording the temperature. Kleitman also states that an evening is as reliable as a morning temperature. Klaften (*J. Clin. Endocrinol.*, **4**:159, 1944) has shown that the intra-uterine temperature is the most reliable, but he considers that for practical purposes the reading of the basal body temperature is sufficient.

Other workers have correlated temperature changes during the menstrual cycle with changes in the ovaries and endometrium. Greulich Morris, and Black (Proc. Conf. Prob. Human Fertility, 1943, p. 37) examined the ovaries in women submitted to laparotomy and found that the fall of temperature about the middle of the cycle is not necessarily evidence of ovulation; the rise which follows does denote ovulation in most cases. The age of the corpora lutea did not always correspond with the temperature readings, perhaps because temperatures were taken only every twenty-four hours or because the rate of development of the corpus luteum varies. Martin (*Am. J. Obstet & Gynec.*, **46**:53, 1943) has checked temperature graphs by endometrial biopsy. He recorded 164 biphasic cycles; in 47 of these biopsy in the second phase showed secretory endometrium. In 17 monophasic cycles, where the rise of temperature in the second half did not take place, there was proliferative endometrium but no evidence of secretory change. Similar findings have been recorded by Halbrecht (*Lancet*, **2**:668, 1945). Martin also demonstrated that the difference in basal body temperature between the two halves of the biphasic cycle was statistically significant, but there was no statistically significant difference in the two halves of the monophasic cycle. The temperature curve is thus a means of distinguishing ovulatory from non-ovulatory menstruation.

This method of determining the time of ovulation needs no expensive apparatus or time-consuming laboratory work. Barton and Wiesner (*Lancet*, **2**:663, 1945) have found it especially useful in helping women to achieve conception—"for example, in the timing of intercourse, the arrangement of leave for Service people, and in artificial insemination." It requires the co-operation of the patient, but this is easily obtained in cases of sterility and in-patients who wish to avoid pregnancy but are unwilling to practise contraception. Further suggested uses for it are a test of early pregnancy, in evaluating treatment intended to stimulate ovulation, in timing the date for endometrial biopsy, and in searching for early ova. Tomkins believes that it should also prove of value in studying irregular uterine hæmorrhage and in assessing the reliability of contraceptive measures.—*Brit. M. J.*, **1**:209, 1946.

NOTES & NEWS

REFRESHER COURSE IN CARDIOLOGY

The Cardiological Society of Bengal, Calcutta, has, in the interest of the medical profession, arranged a series of lectures in Cardiology at the Indian Medical Association, 67, Dharamtala Street, Calcutta. The inaugural address was delivered by Dr. Sunil C. Bose, M.B., M.R.C.P. on the 1st August 1946.

Any information in connection with the course of lectures are obtainable from the office of the Society at 67, Dharmatala Street, Calcutta, between 2 p.m. and 10 p.m. (telephone Calcutta 1570).

PURCHASER'S PERMIT UNDER DRUGS CONTROL ORDER

Government are pleased to decide that an unregistered medical practitioner who may apply for purchaser's permit under the Drugs Control Order, will be granted exemption by the Provincial Government from the payment of the prescribed license fee under the proviso to sub-clause (1) of clause 6 of the said order, provided that the Provincial Licensing Authority certifies that the practitioner has sufficient reputation as a medical man and has built up a wide practice and that the permit is required for the purposes of his practice.

THE TEACHING OF TUBERCULOSIS

The following Memorandum on the Teaching of Tuberculosis to Medical Students has been issued by the Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C., over the signature of Dr. Frederick Heaf (Chairman) and Dr. Harley Williams (Secretary):

No one will deny that the teaching of tuberculosis to medical students is far from satisfactory. It is still only too common an experience to find that a newly qualified practitioner's only acquaintance with tuberculosis is based on physical signs of cases in advanced stages of the disease and a very theoretical knowledge of sanatorium routine. The vast field of the preventive and sociomedical side of the subject and even the importance of early diagnosis are largely unknown to him, so that he enters practice quite unable to appreciate the significance of one of the commonest and most serious diseases.

In the Goodenough Report on Medical Schools it is stated that the present facilities for teaching tuberculosis vary considerably in teaching centres, and it gives two examples which indicate the differences which exist in the nature of the instruction, showing how it depends mainly on the presence or absence of a tuberculosis department or dispensary attached to the hospital of the medical school. The situation as it was in 1939 is summarized at the end of the report. At that date, of the 25 medical schools in England, Scotland, and Wales, 12 provided teaching in tuberculosis, but not in the main hospitals. Of these 12, nine made use of the treatment beds of the local authority. Four teaching hospitals made use of the facilities at special chest hospitals. Only two hospital medical schools had beds of their own reserved specially for tuberculosis cases. It would appear that in over 50% of the medical schools it was only by good fortune and not by any arrangement on the part of the authorities that the student was able to acquire knowledge on tuberculosis. In such schemes where it was possible for the student to take a course in tuberculosis it was usually quite optional and dependent on the personal inclination of the student himself. It not infrequently happened, therefore, that the student passed through his medical training seeing only a few cases of pulmonary tuberculosis, and if he did it would be those with advanced disease, so that the mental picture he formed of the disease would be one of crepitation, rales, and pulmonary cavities, and a hazy idea that all such patients require sanatorium routine with the addition of artificial pneumothorax treatment if it could be given. It is not surprising, therefore, that he does not recognize the disease until it has reached this advanced stage.

A more recent survey made by the Tuberculosis Educational Institute has revealed some improvement in the situation, particularly in the Northern medical schools. In nine teaching schools compulsory courses in tuberculosis are arranged and short periods of residence at the local authority's sanatorium are included in the curriculum. A number of visits are paid to the local dispensary so that the student begins to appreciate the socio-medical side of the problem and the value of early diagnosis. These arrangements all show how necessary it is for educational purposes to link up the tuberculosis services of the local authority with the medical schools. In this matter local authorities might use the old advertisement slogan, "You want the goods—we have them."

The committee of the Tuberculosis Educational Institute has given considerable attention to the undergraduate and postgraduate facilities for studying tuberculosis in all parts of the country, and it feels that the time has come to emphasize the need for putting tuberculosis tuition in a more prominent position in the medical training of the student and to arrange, uniformly in all schools, easy access to the local authorities' tuberculosis services so that the vast amount of material being dealt with at the many dispensaries and sanatoria in the country may be used for teaching of tuberculosis in all its aspects.

The committee strongly supports the recommendation in the Goodenough report that there should be a tuberculosis dispensary at or adjoining every parent teaching hospital and that in-patient facilities for cases of both pulmonary and non-pulmonary tuberculosis should exist in one or more of the hospitals constituting the teaching centre, provided there is a chest physician or orthopœdic surgeon in charge of the beds, or a chest hospital within easy reach. It does not, however, consider that such facilities should exclude from the curriculum a series of visits to sanatoria, for it is almost impossible to convey the meaning of sanatorium treatment to a class of students around the bedside in the wards of a general hospital.

The committee wishes to amplify the scheme of the Goodenough report by suggesting that:

1. The physician in charge of the dispensary and/or the medical superintendent of the sanatorium might with advantage be appointed a lecturer on the staff of the medical school which may be situated within the region or area which the dispensary or sanatorium serves.

2. All medical students must be attached to approved tuberculosis dispensaries as clinical clerks for short periods, during which time they should also become acquainted with the technique and organization of mass radiography.

3. Facilities should be made available for short periods of residence at approved sanatoria for medical students who wish to make a further study of the subject.

It will probably be argued that the medical curriculum is already heavy loaded and it would be difficult to find time for these suggestions. The committee is well aware of this difficulty; but would suggest that those diseases which have the highest incidence should receive priority in a teaching syllabus, even if it meant sacrificing time on the rare conditions which always have a fascination and often assume an exaggerated importance in medical education for a qualifying degree.—*Brit. M. J.*, **1**:60,1946.

VITAMIN CONTENT OF HUMAN MILK

Since milk is the basic food of the infant and many babies are raised on formulæ containing cow's milk adjusted to resemble human milk, a knowledge of the complete chemical composition of both types of milk is desirable. The content of all the grosser constituents such as fat, carbohydrate, protein and minerals is well known. Recently Macy and her associates (*Am. J. Dis. Child.*, **70**:135, 1945) have added to our knowledge of the vitamin content of human milk. In this series of studies the newer microbiologic and chemical procedures were used to determine the concentrations of vitamin A, ascorbic acid, nicotinic acid. biotin, pantothenic acid, thiamine and riboflavin in twenty-four hour samples of human milk. This period of collection was adopted to remove the possibility of diurnal variations. For this study a number of pregnant and lactating women were either given special diets of high vitamin content or allowed to choose their own diets. It was found that the vitamin content of the milk from those women who choose their own diet was lower than those on the planned diets, although the differences were small. Using the values for the vitamin content of human milk which were obtained by the Detroit group, Maynard and his co-workers (*Am. J. Dis. Child.*, **70**:135, 1945) made comparisons with the vitamin content of cow's milk. Human milk was found to be higher than bovine milk in regard to ascorbic acid, nicotinic acid and inositol. Cow's milk was found to contain more thiamine, riboflavin, pyridoxine, biotin and pantothenic acid than human milk. A factor to be taken into consideration when comparing these values is that the normal commercial processing and delivery of cow's milk may cause considerable loss of the riboflavin and ascorbic acid activity.—*J.A.M.A.*, **130**:215, 1946.

ATOMIC RESEARCH AND MEDICINE

In his recent address to the Manchester Joint Research Council Sir John Anderson mentioned the usefulness to medicine of work on the atomic bomb. The technique employed to produce the new element plutonium gave a ready means of procuring a vast range of new radioactive substances. Radio-phosphorus, radio-iron, and radio-sodium, for example, could now be administered in proportions too small to be harmful, and their radio-active properties could be used to determine their exact behaviour in humans and in animals. Work of this kind has been done in many laboratories in the United States during the last five years.

One of the striking developments has been the discovery of the mechanism of transmethylation by Vincent du Vigneaud at Cornell University Medical School in New York. His work leads to the general conclusion that all C-CH and S-CH groups in the tissues of the body originate in the methyl groups of choline, betaine, and methionine. He studied effect on the growth of rats of adding homocystine to a methionine-free diet. Some observers had found that homocystine enabled rats to grow, but du Vigneaud was unable to confirm this. He showed that something in the B complex was necessary as well as homocystine, and finally choline was discovered to be the missing substance. In the presence of choline, homocystine was transformed to methionine, and this effect of choline was because of the methyl groups it contained; tri-ethylcholine had no such effect. Thus the inference was that the growth which resulted from feeding both homocystine and choline was due to the transference of a CH group from choline to homocystine to yield methionine. Proof of this was obtained by preparing choline in which the hydrogen in CH groups was replaced by heavy hydrogen (deuterium). This product, deuteriocholine, was fed to rats together with homocystine; du Vigneaud then sought and found the deuterio-methyl group in the methionine of the tissues. He has shown in the same way that the methyl group of creatine comes from choline or methionine; deuterio-choline given to rats led to the appearance of the deuterio methyl group in the creatine of the muscle and also in the creatinine of the urine. This observation has since been extended to man by feeding heavy methionine and examining the creatinine in the urine. The administration of heavy methionine to rabbits leads to the appearance of deuterio-anserine in the muscle tissue. Dr. George Whipple and his colleagues (*J. Biol. Chem.*, **134**:585, 1940 & *Am. J. Physiol.*, **135**:600, 1940) have used ferric sulphate, ferric chloride, and ferric ammonium citrate containing radio-active iron; the amount present might be 1 part in 2,000 million. They have given a single dose of this so-called "tagged" iron to dogs depleted of iron. This leads to a rise in the proportion of red cells containing tagged iron which reaches a peak between the fourth and the seventh day, after which the proportion declines. If red cells are broken down by giving acetyl phenyl hydrazine it is found (by following the tagged iron) that the iron set free is almost wholly used to make fresh red cells. In dogs with a biliary fistula very little iron is found in the bile; the amount may rise from 0·2 mg. to 2 mg. for a day or two and then diminish, the total iron excreted in the bile being about 15 mg. The total breakdown, however, has been about 450 mg. The formation of liver glycogen in the rat after the administration of lactic acid has been studied by Baird Hastings (*J. Biol. Chem.*, **137**:557, 1941 & *Ibid.*, **142**:371, 1942) at Harvard. There are three carbon atoms in lactic acid, and samples of lactic acid have been prepared in which each of these three carbon atoms in turn was radio-active. Thus it has been possible to find to what extent the three carbon atoms respectively contribute to the formation of liver glycogen.

These examples of the use of radio-active elements can be mulptiplied many times. Thus observations in which radio-active iodine and radio-active phosphorus have been employed have been made by several workers. It is clear that the method provides a new approach to the discovery of the stages of numberless biochemical transformations.—*Brit. M. J.*, **1**:169, 1946.

I.M.A. DISTRESS RELIEF FUND

The Hony. General Secretary, Indian Medical Association, has received, as contribution to the Association's Distress Relief Fund, a sum of Rupees Two hundred only from an anonymous donor which is gratefully acknowledged.

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